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Hemorrhage and Hemorrhagic Shock in Swine: A Review

John P. Hannon

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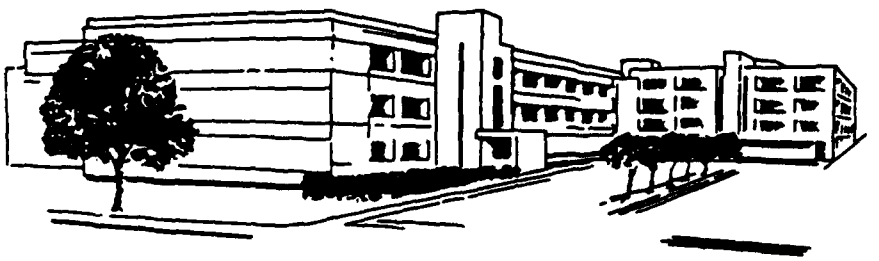

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Hemorrhage and Hemorrhagic Shock in Swine: A Review, J. P. Hannon

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A review of the literature shows that porcine models have been used extensively over the past 20 years to study the effects of hemorrhagic hypotension and shock. In pigs, as in humans, hemorrhage causes a decrease in cardiac output, a primary defect that often leads to a cascade of secondary dysfunctions which are life-threatening. Reduced arterial O_2 delivery to body tissues, a major secondary effect, often leads to anaerobic glycolysis and lactacidemia so severe that death ensues. To offset these potentially life-threatening dysfunctions, conscious pigs, and humans, mobilize a series of compensatory responses, including hyperventilation to improve blood oxygenation and CO_2 elimination, neurohumoral changes to maintain blood pressure and redistribute cardiac output in favor of vital organs such as the brain and heart, enhanced O_2 extraction to support tissue

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O_2 demand, and effective use of blood buffers to minimize adverse effects of lactacidemia.

This review shows that certain experimental manipulations can seriously compromise the effectiveness of porcine hemorrhage models. The use of anesthetics, for example, may lead to a suppression of ventilation and thereby exacerbate the deleterious effects of lactacidemia. Anesthetics also instigate hemodynamic alterations that adversely affect normal compensations. Fixed-pressure hemorrhage models, particularly the classical Wiggers irreversible shock model, oftentimes produce functional defects that have little clinical relevance. In addition, some experimental manipulations such as physical restraint can distort responses to blood loss by mechanisms that are not fully understood.

Swine can be used effectively to simulate the functional effects of hemorrhagic hypotension as it is commonly seen in human trauma victims. Effectiveness of porcine models, however, is significantly enhanced when functional characteristic closely emulate those seen in the conscious trauma victim or the conscious, chronically instrumented animal.

ABSTRACT

A review of the literature shows that porcine models have been used extensively over the past 20 years to study the effects of hemorrhagic hypotension and shock. In pigs, as in humans, hemorrhage causes a decrease in cardiac output, a primary defect that often leads to a cascade of secondary dysfunctions which are life-threatening. Reduced arterial O_2 delivery to body tissues, a major secondary effect, often leads to anaerobic glycolysis and lactacidemia so severe that death ensues. To offset these potentially life-threatening dysfunctions, conscious pigs, and humans, mobilize a series of compensatory responses, including hyperventilation, to improve blood oxygenation and CO_2 elimination, neurohumoral changes to maintain blood pressure and redistribute cardiac output in favor of vital organs such as the brain and heart, enhanced O_2 extraction to support tissue O_2 demand, and effective use of blood buffers to minimize adverse effects of lactacidemia.

This review shows that certain experimental manipulations can seriously compromise the effectiveness of porcine hemorrhage models. The use of anesthetics, for example, may lead to a suppression of ventilation and thereby exacerbate the deleterious effects of lactacidemia. Anesthetics also instigate hemodynamic alterations that adversely affect normal compensations. Fixed-pressure hemorrhage models, particularly the classical Wiggers irreversible shock model, oftentimes produce functional defects that have little clinical relevance. In addition, some experimental manipulations such as physical restraint can distort responses to blood loss by mechanisms that are not fully understood.

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PREFACE

The Author is greatly indebted to Carol A. Bossone who provided major contributions to the development and physiological evaluation of porcine hemorrhage models at Letterman Army Institute of Research. The author also acknowledges the superb efforts of Dr. Charles E. Wade, Dr. John D. O'Benar, Dr. William G. Rodkey, Dr. Virginia L. Gildengorin, Marjorie M. Hunt, Janis A. Loveday, and Robert Coppes in initiating and conducting many cooperative studies.

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INTRODUCTION

Seventy years ago, Mary V. Buell in the Department of Agricultural Chemistry at the University of Wisconsin, became the first investigator to employ swine as an experimental model for studying the functional effects of hemorrhage *(Buell, 1919)*. Using large, market weight (95 to 132 kg) animals, she showed that blood loss was associated with decreases in the alkali reserve and protein nitrogen concentrations of plasma, as well as with increases in plasma nonprotein nitrogen and urea concentrations. Her hemorrhage procedure was simple: she lopped off the end of the tail and collected the shed blood in an Erlenmeyer flask containing oxalate. In most instances, the changes she observed were relatively small, probably because the hemorrhage volumes were small (9-14 ml/kg), but her interpretation of the data was essentially correct. Loss of alkali reserve was attributed to increased hydrogen ion production with a resultant decrease in plasma bicarbonate. Loss of plasma protein was attributed to fluid transfer from the extra- to the intravascular space, and increases in nonprotein nitrogen and urea were attributed to catabolism of body protein. In addition, Dr. Buell showed foresight in designing her experiments to show the rate at which normal compensatory responses could reverse the changes in blood chemistry elicited by hemorrhage; in most instances the pigs reverted to a normal status within a few days.

Nearly 50 years elapsed before pigs were next again used to study the effects of hemorrhagic hypotension and shock, but from the late 1960's to the present time we see a progressive increase in the popularity of porcine biomedical models. In this review I will first consider the various porcine models that have been used in studies of hemorrhagic hypotension, their attributes and their limitations. Subsequently, the major functional changes associated with blood loss will be described. And finally, factors contributing to survival, death and effective resuscitation will be discussed.

HEMORRHAGE MODELS

Most porcine hemorrhage models are based on concepts and procedures previously developed in other species, especially the dog. As a consequence, many of the attributes as well as the deficiencies of canine models have been carried over to those developed in swine. In general, however, porcine hemorrhage models appear to be superior to comparable canine models in terms of their applicability to human oriented physiologic phenomena and clinical

problems *(Hannon and Bossone, 1986; Hobler and Napadono, 1974; Lowery and Sugg, 1971; Phillips, 1989; Traverso et al., 1984b).*

Desired Model Attributes

The ideal biomedical model provides a set of physiological or other characteristics that closely approximate those observed under normal or pathologic conditions in humans. Few models fully achieve this ideal, but some are clearly superior to others. Deficiencies ensue when inadequate attention is paid to the particular human condition, and the specific characteristics of that condition which the model is expected to replicate *(Bellamy et al., 1986)*. This review shows that deficiencies also ensue when intentional or unavoidable constraints are placed on model development and use.

Hemorrhage, as it is seen in human trauma victims, is by far the most common clinical condition in which pigs are now serving as biomedical models. Even though experimental objectives may differ, the majority of investigators use one or the other of two basic models to simulate the clinical characteristics and consequences of blood loss. One of these is the fixed pressure or Wiggers model, the other is the fixed-volume model.

The Wiggers Model

In the classical Wiggers model, blood is rapidly withdrawn from the animal until some predetermined mean arterial pressure is obtained, e.g. 40 mm Hg. Pressure is subsequently maintained at this level for a considerable period of time, sometimes hours, by withdrawal of additional blood or reinfusion of shed blood. At the end of the hypotensive period, all of the shed blood is returned to the animal. Variations of this model are numerous. Blood pressure may be maintained initially at one level of hypotension and subsequently at an even lower level before resuscitation is attempted. In most studies, the animals are anesthetized, and acutely instrumented before experimental manipulations and measurements are attempted; few studies involve chronically instrumented conscious animals.

Attractiveness of the Wiggers model is largely attributable to its reproducibility both within and between investigators and laboratories. In recent years, however, the model has come under increasing criticism for its lack of clinical relevance, particularly when used to study so called irreversible shock; irreversible shock as seen in the Wiggers model is rarely, if ever, seen in combat casualties of trauma victims *(Bellamy et al., 1986; Zweifach and Fronek, 1975)*. Nevertheless, the fixed-pressure model would seem to have some utility if it is used to simulate a clinical condition in

which continued blood loss results in an extended period of hypotension. It should be recognized, however, that this utility can be seriously compromised if shed blood is used to maintain the desired hypotensive level. As amply demonstrated in swine, hemorrhage usually leads to the production of vasoactive (see below) and other materials *(Bonner, 1978; Meagher et al., 1971; Pressler et al., 1980; Smokovitis et al., 1985; Sugg et al., 1971)*. Reinfusion of shed blood, furthermore, would seem to have little, if any, clinical relevance since much of the blood lost following injury is not available or suitable or transfusion .

The Fixed-Volume Model

Use of the fixed-volume model is gaining in popularity because it more closely simulates hemorrhage seen in accident victims or combat casualties *(Bellamy et al., 1986)*. When used in such a context, the model is designed to reproduce a clinical scenario in which rupture of a major vessel leads to blood loss and hypotension, but the degree of hemorrhage is eventually controlled by first aid or other measures. Typically, a predetermined volume of blood is removed from an artery over a predetermined time period, and functional or other changes are then monitored during and subsequent to the period of blood loss. Variations of the model are largely in the form of differences in the rate, pattern and amount of blood removal. Some workers rapidly withdraw the predetermined volume, others do it more slowly, or in stepwise fashion. These variations readily lead to differences in outcome. In our laboratory, we attempt to simulate arterial hemorrhage as it might occur in the accident victim. Blood is thus removed continuously on an exponential scale such that the rate of loss is greater during the early stages of hemorrhage when arterial pressure is high but at progressively slower rates during the subsequent stages as arterial pressure falls *(Hannon et al., 1981b, Hannon and Bossone, 1986)*. As in the Wiggers procedure, some workers implement the fixed-volume model using anesthetized, acutely instrumented animals whereas others use a conscious, chronically instrumented preparation. Unlike the Wiggers procedure, however, few workers using the fixed-volume procedure reinfuse shed blood subsequent to the hemorrhage episode. A mathematical model of cardiovascular function during fixed-volume hemorrhage in swine has been reported by Berman et al. *(1987)*.

Other Models

Neither the fixed-pressure nor the fixed-volume model truly simulate hemorrhagic hypotension as it is commonly seen in trauma victims. These models rarely incorporate the trauma component, largely because of current ethical standards governing the use of animals in biomedical research. Traumatic shock alone, induced by

fractures and soft tissue damage, has been studied in anesthetized pigs *(Blomquist et al., 1989; Rokkanen et al., 1974)*, but insofar as this author is aware, only Almskog and coworkers *(1984)* have studied the combined effects of hemorrhage and trauma (gunshot wound) in pigs. They found that moderate hypovolemia in anesthetized animals markedly increased the metabolic deterioration around a high velocity missile tract in skeletal muscle, but the presence of such muscle injury did not alter the eventual effectiveness of volume restitution in reversing the hemodynamic dysfunctions associated with hypovolemia. Limited efforts have been made to simulate at least some of the physiologic or psychologic features of trauma as they might affect responses to hemorrhage. O'Benar *(1988)*, for example, simulated nociceptive input by stimulating the sciatic nerve during fixed-volume hemorrhage of anesthetized pigs; variable results were obtained. Wade and Hannon *(1988)*, and more recently Carlson et al. *(1989)*, evaluated the effects of mild stress, induced by physical restraint; qualitative and quantitative alterations in the hemodynamic responses and to blood loss were observed. Porcine models incorporating combined insults have included the interactions of intracerebral pressure and hemorrhage *(Pfenninger et al., 1984, 1985, 1986)*, hemorrhage and dehydration or rehydration *(Barrientos et al., 1982)*, and hemorrhage associated with ethyl alcohol intoxication *(Zink et al., 1988)*.

A potential deficit in most current models centers around the procedures used in effecting and controlling hemorrhage. Almost invariably, blood is removed from the animal by means of an indwelling venous or arterial catheter. Human hemorrhage victims, in contrast, bleed from a traumatically ruptured blood vessel, a circumstance that often allows normal compensatory responses (clot formation, vascular constriction) to limit the amount of blood actually lost. Only recently has a porcine model been developed to address these responses and their potential impact on clinical resuscitation regimens *(Bickell et al., 1987, 1989)*. Sometimes hemorrhage cannot be controlled and the trauma victim bleeds to death. Continuous exsanguination models to simulate this circumstance have been developed by Smokovitis et al. *(1985)* and *Syverud et al. (1987, 1989)*.

Anesthetics

Use of anesthetics in the implementation of porcine hemorrhage models presents a variety of perplexing issues that can never be totally resolved. Anesthetic agents are often used to eliminate pain associated with the surgical procedures needed to prepare the animal for study. Sometimes the experimental procedure itself inflicts pain and anesthetics must be used. Such uses are

justifiable, in fact are mandated, for the ethical use of animals in any experimental setting. Oftentimes, however, it would appear that anesthetics are used solely as a convenience to the investigator; it is far easier to acutely instrument and study an anesthetized animal than to chronically instrument and study a conscious animal. In terms of clinical relevancy, however, hemorrhage in humans, at least initially, usually occurs while the victim is conscious.

It is now well established in species other than pigs that anesthetic agents produce functional alterations that not only enhance the adverse effects of hemorrhagic hypotension, but also compromise normal compensatory responses to blood loss *(Zweifach and Hershey, 1949, Zweifach, 1975)*. In swine, Simon and Olsen *(1969a, 1969b)* showed many years ago that pentobarbital anesthesia led to a marked increase in sensitivity to blood loss, and that this effect was attributable to anesthesia-induced decrements in capillary blood flow to vital organs such as the heart. They also showed that pentobarbital compromised the hemodynamic responses to vasoactive agents in hypovolemic pigs *(Olsen, 1969)*. More recently, Weiskopf and his colleagues have conducted detailed investigations of the cardiovascular, pulmonary, endocrine and metabolic effects of anesthetic agents when administered to hypovolemic pigs. These agents included enflurane, halothane, isoflurane, and ketamine *(Weiskopf et al., 1981)*, ketamine and thiopental *(Weiskopf et al., 1984)*, ketamine and thiopentone *(Weiskopf and Bogetz, 1985a)*, and halothane and nitrous oxide *(Weiskopf and Bogetz, 1985b)*. All of these anesthetics distorted the functional changes associated with blood loss and compromised the compensatory responses that normally facilitate survival of the hypovolemic animal.

The Use of Immature Pigs

As noted by Phillips *(1989)*, the vast majority of porcine biomedical models utilize immature domestic pigs as the experimental animals, and results obtained with these animals are frequently extrapolated to the human adult. The literature on porcine hemorrhage, for example, contains only occasional reports in which mature domestic *(Buell, 1919)* or miniature *(Buckley, 1986b; Gaskill et al., 1984a, 1984b; Hottenrott et al., 1977, 1978; Laughlin, 1983; Levine et al., 1979, 1983)* pigs served as experimental animals. The legitimacy of extrapolating results obtained from 1 to 3 month old animals to the adult human can be questioned *(Phillips, 1989)*. Specifically, do immature pigs display the same functional characteristics as adult pigs?

Most reports on circulatory maturation in the pig are based on animals ranging in age from a few hours to about one month. *Marini et al. (1968) and Boncompagni et al. (1968)* were the first

investigators to use porcine hemorrhage models to study this subject, and most of the subsequent literature has been reviewed by Buckley et al. *(1983, 1984, 1988)* and Gootman and her colleagues *(Gootman, 1986; Gootman et al., 1981, 1983, 1986)*. A few reports address circulatory maturation in the porcine fetus *(Biermann et al., 1979; Macdonald et al., 1986; Pipkin et al., 1981)*. Collectively, the reported studies show that most circulatory functions are fully developed at birth. A few mature during the early stages of infancy. Thus, when the typical two to three month old splenectomized pig is used as a biomedical model, one obtains responses to hemorrhage that are remarkably similar to those reported for adult humans *(Hannon and Bossone, 1986)*.

Many of the functional changes associated with hemorrhage in swine have been studied in some detail while others have received only limited attention. In reviewing these changes I will attempt to identify experimental or other variables that can qualitatively or quantitatively affect outcome. For reference purposes, data collected from conscious pigs will be used to illustate the functional alterations associated with a lethal, fixed-volume hemorrhage; responses obtained with this model will be compared to those obtained from other models.

The fixed-volume procedure used in the author's laboratory was developed about 10 years ago, initially to determine the physiologic characteristics of hemorrhagic hypotension in a conscious porcine model *(Hannon et al., 1981a, 1981b, 1981c; Hannon and Bossone, 1986; Hannon and Skala, 1982; Wade and Hannon, 1988)*. More recently it has been used, sometimes in modified form, to facilitate efficacy studies of various resuscitation procedures, a subject that will be considered in more detail later. The data reported here were obtained from a control group of pigs that were resuscitated (ineffectively) with a 4 ml/kg bolus of normal saline. Specific procedures and methods used in implementing this model are contained in reports by Hannon et al. *(1981b, 1982, 1989a, 1989b)*, Hannon and Bossone *(1986)*, and Wade et al. *(1989a)*. Briefly, 7 to 10 days before study, 8 pigs were splenectomized, chronically instrumented with carotid and pulmonary artery catheters, and trained to accept a respiratory mask and physical restraint in a Pavlov sling. On the day of study, following a rest period of 30 to 60 minutes, control measurements were made in duplicate at 10 min intervals. Immediately thereafter, blood was progressively removed from the carotid catheter using an exponential scale such that 7.5 ml/kg increments were withdrawn after 9, 19, 31.5, 44, and 60 min; total blood loss was 37.5 ml/kg. All measurements were repeated at each of the foregoing time points and at 5 and 15 min

subsequent to hemorrhage; death of the animals precluded additional post-hemorrhage measurements *(Wade et al., 1989a)*.

HEMODYNAMIC EFFECTS OF HEMORRHAGE

Cardiac Output

Moderate to severe blood loss in swine invariably leads to a decrease in cardiac output, a key dysfunction that is responsible, either directly or indirectly, for all of the other functional changes that are seen during or subsequent to hemorrhage. Fig. 1 illustrates the cardiac output changes seen in our lethal fixed-volume model. Similar results, although differing in degree, are reported for other fixed-volume models *(Bellamy et al., 1984b; Carlson et al., 1989; Chudnofsky et al., 1989a; DiStazio et al., 1980; Hobler and Napodano, 1974; Shackford, et al., 1988a; Traverso et al., 1987; Weiskopf et al., 1986)*, as well as for Wiggers models *(Burghuber et al., 1977; Faenza et al., 1982b; Fredlund et al., 1974; Levine et al., 1978)* and uncontrolled or continuous hemorrhage models *(Bickell et al., 1987, 1989; Syverud et al., 1989)*.

The magnitude of the cardiac output decrement seen in hypotensive swine can be influenced by a number of experimental variables. The particular measurement technique, however, does not appear to be a critical factor; Levine and Sirinek *(1981)* report nearly identical changes in output when measured by three different procedures. Rate and magnitude of blood loss, on the other hand, can have a major effect. Rapid loss, as in the Bickell procedure *(Bickell et al., 1987)*, leads to a much greater reduction in cardiac output than that illustrated in Fig. 1, even though much more blood is lost in our fixed-volume model. Similar effects are seen in experimental results reported by Traverso et al. *(1985a)*. Anesthetics also can have a major effect, producing an additional reduction in cardiac output over that seen in the conscious animal *(Weiskopf and Bogetz, 1985b; Weiskopf et al., 1984)*. Training regimens used to familiarize conscious animals with physical restraint may also have a significant effect; thoroughly trained pigs, for instance, show a greater reduction in cardiac output to a given volume of hemorrhage than inadequately trained pigs *(Carlson et al., 1989)*. Such a difference could be due to greater muscular activity with consequently greater venous return on the part of the more poorly trained animals.

Decrements in cardiac output during hemorrhage are attributable primarily to a reduction in venous return. This reduction is evidenced by lowered values for central venous pressure *(Carlson et al., 1989; Chudnofsky et al., 1989b; Laughlin, 1983;*

LeGal, 1983; Shackford et al., 1988a, 1988b; Stremple et al., 1976; Ziegler et al., 1987), right atrial pressure *(Weiskopf and Bogetz, 1985b; Weiskopf et al., 1984, 1986)*, right atrial volume *(Carlson et al., 1989)*, pulmonary capillary wedge pressure *(LePage et al., 1984; Weiskopf et al., 1986)*, and left atrial pressure *(Bellamy et al., 1984b; Traverso et al., 1985a, 1987)*.

Stroke Volume

As a consequence of reduced venous return, stroke volume falls during hemorrhage. In our lethal fixed-volume model, for example, stroke volume values recorded at the end of hemorrhage are less than one-half of those recorded during the control period (data not shown). At least qualitatively, similar effects are seen in other fixed-volume models *(LePage et al., 1984; Maningas, 1987; Shackford et al., 1988a; Weiskopf et al., 1984; Weiskopf and Bogetz, 1985b)*, and in the uncontrolled hemorrhage model *(Bickell et al., 1989)*. Insofar as can be determined, stroke volume changes have not been reported specifically for pigs subjected to a fixed-pressure (Wiggers) hemorrhage protocol, but decrements become apparent if cardiac output values recorded during hemorrhagic hypotension are divided by heart rate. The magnitude of the stroke volume change, as might be anticipated, is roughly proportional to the decrease in cardiac output, but can be influenced by hemorrhage-induced changes in heart rate; for a given decrement in cardiac output, the change in stroke volume is inversely related to the change in heart rate.

Heart Rate

Depending upon the hemorrhage model and the experimental conditions associated with a study, blood loss can lead to an increase, decrease or no change in heart rate. Unchanged values are often seen when conscious, unrestrained pigs are subjected to a progressive, but nonlethal, fixed-volume hemorrhage *(Bellamy et al., 1984b; Hannon et al., 1981b, 1986; Traverso et al., 1985a; Wade and Hannon, 1988)*. In some instances, the values may actually decrease during the course of a prolonged, nonlethal hemorrhage, but such episodes are followed by tachycardia during the recovery period *(Hannon and Bossone, 1986)*. Unrestrained conscious pigs also exhibit tachycardia if the hemorrhage insult leads to a lethal outcome *(Bellamy et al., 1984b; Maningas, 1987; Traverso et al., 1986a, 1986b, 1987)*. Pigs trained to accept physical restraint show a similar response (Fig. 1); in fact, tachycardia may be seen in restrained animals even though the hemorrhage is nonlethal *(Wade and Hannon, 1988)*. Other factors or conditions that seem to predispose conscious pigs to tachycardia during hemorrhage include splenectomy *(Wade and Hannon, 1988)*, rapid blood loss *(Bickell et al., 1987, 1989; LeGal, 1983; DiStazio et al., 1980; Rowe and Uribe,*

1972), neuromuscular blockade *(Weiskopf and Bogetz, 1985b; Weiskopf et al., 1984, 1986)*, and hyperthermia *(Wade and Hannon, 1988)*. Tachycardia is always observed when anesthetic agents are used, even with mild hemorrhage, *(Buckley et al., 1984, 1986b; Chudnofsky et al., 1989b; LePage et al., 1984; Maier et al., 1981)*, or when the Wiggers procedure is used to study the effects of sustained hypotension *(Laughlin, 1983; Moosa et al., 1978; Nagasue et al., 1974; Rudehill et al., 1987)*. Heart rate remains unaltered during a slow, prolonged hemorrhage even though a large amount of blood may be removed *(Lehtola et al., 1986)*.

Myocardial Performance

There is little or no evidence of a deterioration in myocardial performance when conscious pigs are subjected to nonlethal or potentially lethal blood loss. In these animals, as in human accident victims, potentially lethal insults can be readily reversed with effective resuscitation procedures *(Bellamy et al., 1986)*. Such reversal is effected by an increase in cardiac output to normal or above normal levels (see below). The lack of performance decrements in the conscious, fixed-volume model may be due to a reduction in myocardial work during hemorrhage *(Wade et al., 1989a; Weiskopf et al., 1985b)* with a concomitant reduction in myocardial O_2 requirements *(Bellamy et al., 1984b)*. These effects are attributable to the reduced pressure head against which the heart must pump. Myocardial performance may deteriorate, however, when the Wiggers procedure is used to study so called "irreversible shock;" a 66% decrease in myocardial contractility is reported when shed blood is reinfused following a sustained period of hypotension *(Bonner et al., 1978; Angelakos and Bonner, 1979)*.

Tissue and Organ Blood Flow

As would be anticipated, reduced cardiac output during hemorrhage leads to lowered blood flow to body tissues. Not all tissues, however, are affected equally, a subject that was first addressed in pigs by Simon and Olsen *(1969a, 1969b)*. They used tissue ^{42}K uptake to investigate nutritive (capillary) blood flow in conscious, chronically instrumented animals subjected to two levels of fixed volume hemorrhage. Their data show a decrease in the gastric fraction of cardiac output following 20% blood loss, with this effect becoming more pronounced if blood loss is increased to 40%. In addition, the more severe hemorrhage also leads to significant decrements in fractional flows to the kidney cortex, skin and muscle, but not to the myocardium, small intestine, kidney medulla or hepatic artery. During hemorrhage, therefore, the data reported by Simon and Olsen *(1969a)* show that cardiac output is redistributed in favor of vital organs such as the heart.

Of perhaps equal importance, the investigations of Simon and Olsen *(1969b)* show convincingly that anesthetics can have a major effect on the distribution of cardiac output. Following pentobarbital anesthesia in the normovolemic animal, they report decrements in fractional flow to the myocardium, kidney medulla and cortex, hepatic artery, gastric serosa and muscularis, skeletal muscle, and adrenal, but little or no change in flow to the skin, gastric mucosa and submucosa, and small intestine. During hemorrhage, their data show that anesthesia significantly exacerbates the fractional flow decrements to many tissues including the myocardium, thus impairing the ability of the animal to compensate for blood loss.

Subsequent workers have confirmed and extended the observations of Simon and Olsen, reporting blood flow measurements, both fractional and absolute, to many different organs and tissues, under a variety of experimental conditions. Transducer based measurements have thus revealed hemorrhage-induced flow decrements in vascular beds supplied by the femoral *Buckley et al., 1984, 1986a; (Burghuber et al., 1977; Gootman et al., 1981, 1983)*, renal *(Buckley et al., 1984, 1986a; Coli et al., 1981b; Gootman et al., 1981, 1983; Reddy et al., 1974; Sondeen et al., 1989b)*, mesenteric *(Burghuber et al., 1977; Gootman, 1981, 1983)*, carotid *(Buckley et al., 1984; Gootman et al., 1981; Reddy et al., 1974)* and hepatic *(Lindberg, 1977; Lindberg and Darle, 1977a, 1977b; Mäkisalo et al., 1988)* arteries. Decrements in portal vein flow also are reported *(Lindberg, 1977; Lindberg and Darle, 1977a, 1977b; Mäkisalo, 1988; Mäkisalo et al., 1988)*.

Radiolabelled microspheres have been widely used to assess capillary blood flow during hemorrhagic hypotension, and reduced flows are reported for a number of tissues, including: the myocardium *(Bellamy et al., 1984b; Laughlin, 1983)*, brain *(Laughlin, 1983; Maningas, 1987; Laptook et al., 1983; Ramenofsky et al., 1981)*, eye *(Ramenofsky et al., 1981)*, kidney *(Bellamy et al., 1984b; Binder et al., 1986; Laughlin, 1983; Leholta et al., 1986; Maier et al., 1981; Maningas, 1987; Ramenofsky et al., 1981; Talja et al., 1986)*, hepatic artery *(Laughlin, 1983)*, stomach *(Gaskill et al., 1984a, 1984b; Hottenrott et al., 1978; Kivilaakso et al., 1974, 1982; Lehtola et al., 1986; Levine et al., 1978, 1979, 1983; Ramenofsky et al., 1981; Seufert et al., 1979)*, intestines *(Bellamy et al., 1984b; Maningas, 1987; Lehtola et al., 1986; Ramenofsky et al., 1981)*, spleen *(Laughlin, 1983; Lehtola et al., 1986; Ramenofsky et al., 1981)* pancreas *(Bellamy et al., 1984b; Maningas, 1987; Ramenofsky et al., 1981)*, skeletal muscles *(Bellamy et al., 1984b; Laughlin, 1983; Maningas, 1987; Ramenofsky et al., 1981)*, thymus *(Ramenofsky et al., 1981)*, skin *(Bellamy et al., 1984b; Laughlin, 1983; Maningas,*

1987; Ramenofsky et al., 1981), pituitary *(Laughlin, 1983)*, and adipose tissue *(Bellamy et al., 1984b; Maningas, 1987)*.

In some instances, usually when the hemorrhage insult is modest, unaltered tissue blood flows are recorded. Normal flows are thus reported for the myocardium *(Gootman et al., 1981; Simon and Olsen, 1969a)*, brain *(Armstead et al., 1988; Leffler et al., 1986; Matsuda et al., 1988)*, stomach *(Lehtola et al., 1986)*, and hepatic artery *(Bellamy et al., 1984b; Lehtola et al., 1986; Matsuda et al., 1988; Ramenofsky et al., 1981)*. Occasionally, absolute increases in tissue blood flow during hemorrhage are reported, for example in portions of the brain *(Ramenofsky et al., 1981)*, left ventricle *(Ramenofsky et al., 1981)*, diaphragm *(Bellamy et al., 1984b; Maningas, 1987)*, and adrenals *(Simon and Olsen, 1969a)*.

Systemic Vascular Resistance

As illustrated in Fig. 1, systemic vascular resistance may decrease, or show little change, when conscious, chronically instrumented pigs are subjected to fixed-volume hemorrhage. Comparable results with conscious fixed-volume models are reported by Bellamy et al. *(1984b)* and Sondeen et al. *(1989a)* and in the uncontrolled hemorrhage model by Bickell *(1989)*. Decrements in systemic vascular resistance are also seen in the report of Syverud et al. *(1989)* in which pigs are bled to death while lightly anesthetized with nitrous oxide. In pigs anesthetized with halothane and nitrous oxide, Fredlund et al. *(1974)* report little change in peripheral resistance during, or after, a relatively short period (30 min) of sustained hypotension. In contrast, increases in systemic vascular resistance are observed when conscious pigs are studied one day after instrumentation for hemodynamic measurements *(Stremple et al., 1976)* or when they are hemorrhaged while paralyzed with succinylcholine *(Weiskopf and Bogetz, 1985b; Weiskopf et al., 1984, 1986)*. Anesthetics such as pentobarbital *(Salerno et al., 1981)* and thiopentone *(LePage et al., 1984)* predispose pigs to an increase in systemic vascular resistance, but mechanical ventilation of chemically restrained pigs does not appear to be an important variable, at least in terms of determining the qualitative nature of the response. Subsequent to hemorrhage, resistance may increase if the insult is lethal *(Bellamy et al., 1984b; Syverud et al., 1989)*.

Resistance changes in regional vascular beds also are reported. In conscious, chronically instrumented domestic pigs subjected to potentially lethal hemorrhage, Bellamy et al. *(1984b)* thus recorded vascular resistance decrements for the brain, diaphragm, renal medulla, hepatic artery and small intestine, no change in vascular resistance for skeletal muscle and skin, and an increase in the

vascular resistance of the pancreas and renal cortex. On a much more limited scale, similar results are reported for other models and experimental conditions. Decreases in resistance are usually seen in vital organs such as the heart *(Bellamy et al., 1984b; Reddy et al., 1974)* and brain *(Armstead et al., 1988; Bellamy et al., 1984b; Buckley et al., 1984; Gootman et al., 1981, 1983; Leffler et al., 1986)*. Because of these resistance decrements, cardiac output during hemorrhagic hypotension is redistributed in favor of the vital organs, even when cardiac output is so depressed that absolute flow to these organs is actually reduced *(Bellamy et al., 1984b; Maningas et al., 1987)*. Such redirection of blood flow is at the expense of less vital tissues. Thus, resistance decremants to vital organs are accompanied by resistance increments in the gastrointestinal tract *(Bellamy et al., 1984b; Gootman et al., 1981, 1983)*, kidneys *(Buckley et al., 1984, Reddy et al., 1974; Sondeen et al., 1989b)* and extremities *(Bellamy et al., 1984b; Gootman et al., 1981, 1983)*.

PULMONARY FUNCTION

Ventilation

Hemorrhage elicits a number of compensatory responses that are directed at alleviating or reversing dysfunctions resulting from a decrease in cardiac output. The above indicated increase in heart rate is one such response. Hyperventilation is another that is commonly seen but only occasionally recorded. In conscious animals subjected to fixed-volume hemorrhage, appropriate measurements reveal sizeable increases in expired minute volume (Fig. 2), alveolar ventilation, and the alveolar ventilation-perfusion ratio *(Hannon et al., 1989b)*. These changes, in turn, produce an increase in arterial PO_2 (Fig. 2), a compensation that facilitates a modest improvement in arterial O_2 content and delivery. Hyperventilaton in the hemorrhaged animal also facilitates CO_2 removal from mixed venous blood, an important variable in the regulation of acid-base status (see below). In the conscious pig, increases in both breathing frequency and tidal volume contribute to the hyperventilatory response *(Hannon et al., 1989b)*.

Literature reports on pulmonary function are difficult to interpret because most investigations were conducted with anesthetized animals, often with mechanical ventilatory assistance. In fact, the author found only one article containing data from conscious animals, a study by Shackford et al. *(1988a)*. These investigators report little or no change in intrapulmonary shunt fraction (Q_s/Q_t) or extravascular lung water in pigs subjected to a modest (28ml/kg) fixed-volume hemorrhage; no other pulmonary variables were measured. In our conscious, fixed-volume model,

shunt fraction decreases slightly during hemorrhage, but returns to normal following effective resuscitation *(Hannon et al., 1989b)*.

Spontaneously breathing anesthetized pigs can respond to blood loss with increases in expiratory minute volume *(Lowery and Sugg, 1971; Lowery et al., 1970)*, but the magnitude of the response is usually attenuated by the anesthetic agent. Ventilatory rate may increase *(Lowery et al., 1970)* or show little change *(Syverud et al., 1989)*. Inadequacy of spontaneous breathing is suggested by markedly lower arterial PO_2 values that are recorded during hemorrhagic hypotension in anesthetized animals *(Pfenninger et al., 1986)*. As a consequence, many investigators mechanically ventilate their animals, often with supplemental oxygen.

Pulmonary Hemodynamics

As would be anticipated, reduced values for pulmonary artery pressure are seen in all studies of hemorrhage in which the appropriate measurements were made. Few studies of porcine hemorrhage, however, include measurements of pulmonary vascular resistance, and the available data are conflicting. Reduced values are reported by Bickell et al. for conscious *(1987)* and anesthetized *(1989)* pigs subjected to aortotomy with uncontrolled blood loss. In the conscious, fixed-volume model we see little change in pulmonary vascular resistance (unpublished data). In contrast to these observations, Weiskopf and his colleagues *(1984, 1985b, 1986)* report increased pulmonary vascular resistance values for conscious pigs subjected to fixed-volume hemorrhage while restrained with a neuromuscular blocker and mechanically ventilated. Similar increments during fixed-volume hemorrhage are reported by Moosa et al. *(1978)* for anesthetized, mechanically ventilated pigs, but the resistance increase was not accompanied by changes in shunt fraction or extravascular lung water. In a similar model, Blomquist et al. *(1989)* also report a resistance increase, but their data show the effect to be statistically insignificant. Burghuber et al. *(1977)* indicate that pulmonary vascular resistance increases progressively during the course of stepwise blood removal from anesthetized pig with reversion of the values toward normal during the hypotensive period subsequent to hemorrhage; again, it is not clear that these effects are statistically significant.

The Wiggers model produces changes in pulmonary function that are rarely, if ever, seen in the fixed-volume model. The fixed-pressure procedure, in fact, is sometimes used to implement studies of shock-induced pulmonary damage. These studies show that a marked increase in extravascular lung water can be induced by prolonged periods of hemorrhagic hypotension followed by reinfusion of shed blood *(Noble, 1975)*. Prolonged hypotension and reinfusion

of shed blood also lead to distortion of pressure-volume and ventilation-perfusion characteristics, and decrements in arterial PO_2 *(Martin et al., 1971; Lowery and Sugg, 1971)*. Lowery and Sugg *(1971)* attribute these dysfunctions, at least in part, to platelet aggregation and blockage of some portions of the pulmonary vascular bed. Support for this conclusion is found in observations of Burghuber et al. *(1977)* who report increases in pulmonary vascular resistance that are negatively correlated with arterial platelet count during a stepwise reduction in blood volume. Blomquist et al. *(1989)* indicate that pulmonary platelet trapping occurs following muscle trauma but not following modest, fixed-volume blood loss. In addition, Smokovitis et al. *(1985)* suggest that changes in the plasma concentrations of plasminogen activator activity and plasmin during hemorrhage may lead to a deposition of fibrin in the pulmonary vascular bed. Fibrin deposition, if it occurs, would be expected to cause an increase in pulmonary vascular resistance. Faenza et al. *(1982a, 1982b)* attribute the resistance increments seen during hemorrhagic hypotension to changes in blood viscosity, but unfortunately they provide no information on their experimental model.

TRANSCAPILLARY REFILL

Perturbations of microcirculatory Starling forces during hemorrhage lead to fluid transfer from the extra- to intravascular space, another major compensatory response that serves to replenish blood volume. In our splenectomized, fixed volume hemorrhage model, this fluid shift is evidenced by a progressive decrease in hematocrit level (Fig.3). These hematocrit changes, furthermore, can be used to calculate the magnitude of transcapillary refill in the hypovolemic animal. In our lethal model, such calculations show that about 13 ml/kg of fluid is transferred from the extra- to the intravascular compartment during the course of the hemorrhage episode. Thus, transcapillary refill replenishes nearly one-half of the plasma (Fig. 3) and over one-third of the blood (data not shown) that is lost during hemorrhage. Fluid transfer is enhanced by an increase in plasma, and presumably interstitial osmolality, and is limited by a progressive dilution of plasma protein (data not shown) with a resultant decrease in plasma oncotic pressure (Fig.3). Other investigators report similar changes in osmolality *(Hannon and Bossone, 1986; Maningas et al., 1986; Peters et al., 1986; Shackford et al., 1988a; Traverso et al., 1987; Wade et al., 1989a; Wright and Henderson, 1975)* and colloid oncotic pressure *(Hannon and Bossone, 1986; Peters et al., 1986; Wade et al., 1989a)*. A small portion of the osmolality increase is attributable to hyperglycemia *(Carey and Wallack, 1970; Chudnofsky et al., 1989b; Hannon and*

Bossone, 1986; Stremple et al., 1976; Syverud et al., 1987; Wade et al., 1989a). Components of the larger portion remain to be identified, but could include metabolites such as urea, amino acids, and fatty acids *(Hannon and Bossone, 1986).*

Studies with other porcine models have shown that the magnitude and pattern of transcapillary refill can be influenced by experimental conditions imposed prior to, or during, hemorrhage. If the animals are dehydrated before study, the magnitude of transcapillary refill will be reduced, at least in conscious animals *(Barrientos et al., 1982).* The degree of training to accept physical restraint during study also influences the magnitude of transcapillary refill subsequent to, but not during, hemorrhage *(Carlson et al., 1989).*

METABOLIC FUNCTIONS

Oxygen Consumption

As illustrated in Fig. 4, hemorrhage in conscious animals initially leads to an increase in O_2 consumption. We attribute this response in large measure, if not entirely, to muscle activity presumably directed toward an enhancement of venous return *(Hannon et al., 1989b).* Similar increases in O_2 consumption are also reported for conscious animals by Weiskopf and his colleagues, but they offer no explanation for the effect *(Weiskopf and Bogetz, 1985b; Weiskopf et al., 1984, 1986).* In their experiments, an elevation of muscle activity would seem unlikely since a neuromuscular blocker was used to restrain the animals. In species other than pigs, there are numerous reports of reduced or unchanged total body O_2 consumption during hemorrhagic hypotension, but in almost all instances the studies were conducted in anesthetized animals *(Hannon et al., 1989b).* One report shows an unaltered O_2 consumption in anesthetized pigs subjected to fixed-volume hemorrhage *(Hobler and Napodano, 1974).* Generally, investigators reporting decrements in energy metabolism attribute the response to inadequate O_2 delivery. However, it should be recognized that most anesthetics suppress muscle activity and reduce the metabolic rate of normovolemic animals, hence it would seem likely that anesthesia predisposes an animal to hypometabolism during hemorrhage. Anesthetics also compromise acid-base regulation during hemorrhage (see below), and if uncompensated acidosis ensues, it could suppress the calorigenic actions of catecholamines *(Hannon et al., 1989b).* Further studies of total body bioenergetics are obviously needed to clarify these issues.

Since lactacidemia is a common finding in all hemorrhage models, it is clear that the O_2 demand of some organs and tissues is not being adequately met during hemorrhagic hypotension. At the present time, however, we have only limited knowledge about the specific organs and tissues that are inadequately oxygenated. Decrements in liver O_2 consumption are reported for anesthetized pigs subjected to prolonged, fixed-pressure hypotension *(Lindberg and Darle 1977a, 1977b; Mäkisalo et al., 1988)*. Under similar circumstances, decrements in cerebral O_2 consumption and glucose utilization also are reported *(Matsuda et al., 1988)*. These responses, however, may be unique to the Wiggers model. Accordingly, unaltered values for cerebral O_2 consumption are reported for conscious pigs subjected to fixed volume hemorrhage *(Armstead et al., 1988; Leffler et al., 1986)*. It would seem likely that skeletal muscle, because of its sheer mass, could be a major contributor to the decrement in O_2 consumption seen in some hemorrhage studies, but few efforts have been made to study the O_2 supply/demand relationships in this tissue. We do know that reinfusion of shed blood, as is often done in the Wiggers model, can have a deleterious effect on the metabolism of skeletal muscle. Thus, Pressler et al. *(1980)* report a decrease in the O_2 consumption of a hindlimb preparation when it is perfused with shed blood and attribute this effect to platelet aggregation and compromised capillary flow. The effect of reduced blood flow alone, as it occurs in fixed volume hemorrhage, has not been studied in a porcine isolated muscle preparation. In fact, studies of O_2 supply/demand relationships across all of the major vascular beds, and the factors affecting these relationships, are clearly needed to ascertain the contributions of various organs and tissues to total body energy metabolism during hemorrhagic hypotension.

Arterial Oxygen Transport

Hemorrhagic hypotension almost invariably leads to a reduction in arterial O_2 transport, although the effect is infrequently reported *(Bickell et al., 1989; Chudnofsky et al., 1989a, 1989b; Hannon et al., 1989b)*. The transport decrements seen in our lethal, fixed-volume model, are illustrated in Fig. 4. These decrements are caused in part by a decrease in cardiac output (Fig. 1) and in part by a decrease in the O_2 carrying capacity of the blood (Fig 4). The fall in O_2 capacity is attributable to transcapillary refill with a resultant lowering of hemoglobin concentration. Under these circumstances, tissue O_2 demand must be met by an increase in O_2 extraction from the circulating blood *(Chunofsky et al., 1989b; Hannon et al., 1989b)*. A widening of the arteriovenous difference in O_2 content is therefore observed (Fig. 4). Similar widening of the arteriovenous O_2 difference during hemorrhage is reported by Bickell et al. *(1989)*, Hannon et al. *(1989b)*, Hobler and Napodano *(1974)*, Moosa et al.

(1978) and Weiskopf et al. *(1986)*. This compensation, however, is limited by the approach of mixed venous O_2 content to near zero values. When this limit is reached, O_2 economy is adversely affected. In short, tissue O_2 demand begins to outstrip O_2 delivery, and energy demand must be met by anaerobic metabolism.

Intermediary Metabolism

Hemorrhagic hypotension may also lead to significant alterations in cellular metabolism. These cellular effects have been studied extensively in other species, especially the rat, but to only a limited extent in swine. Porcine studies, furthermore, have been concerned almost exclusively with the effects of hemorrhage on carbohydrate metabolism. As in other species, the lactacidemia seen in swine reflects an aerobic to anaerobic shift in cellular glucose catabolism. This shift to anaerobic glycolysis presumably occurs in tissues, such as skeletal muscle, that are poorly perfused during hypotension, but insofar as can be determined, few efforts have been made to provide direct evidence of the magnitude of specific tissue contributions to the total body lactate pool. This evidence can be obtained by simultaneous measurements of tissue blood flow and arteriovenous differences in lactate concentration in the major vascular beds of hypotensive swine. Such measurements would also identify tissues that utilize lactate as an energy yielding substrate during hemorrhagic hypotension. An example of this experimental approach is seen in the report of Stremple et al., *(1976)*,in which myocardial glucose utilization and lactate production were measured during and subsequent to a fixed volume hemorrhage; a shift toward anaerobic glucose utilization is observed. Another example is seen in the report of *Mäkisalo (1988)* who showed by transhepatic measurements that liver lactate uptake remains unaltered even during extended periods of fixed-pressure hemorrhagic hypotension.

Hemorrhagic hypotension in swine also leads to hyperglycemia, a response that is attributable to increased adrenal epinephrine secretion with a resultant activation of hepatic phosphorylase and a breakdown of liver glycogen to glucose *(Carey and Wallack, 1970; Carey et al., 1972; Wright and Henderson, 1975)*. The role of this added glucose in supporting tissue energy needs is somewhat controversial. Wright and Henderson *(1975)* show that free glucose accumulates in the red blood cells and muscle tissue of hypotensive pigs and that these changes are accompanied by increases in plasma insulin and phosphate levels. Based on this evidence, they suggest that hemorrhagic hypotension may lead to a reduction in tissue phosphorylation and glucose catabolism. Stremple et al. *(1976)*, on the other hand, provide direct evidence of increased glucose utilization by the myocardium of hypotensive pigs.

Little is known about the effects of hemorrhagic hypotension on protein and lipid metabolism of swine. The plasma concentration of nonprotein nitrogen tends to rise following blood loss *(Buell, 1919)* as does creatinine *(Coli et al., 1981b; Hannon and Skala, 1982; Hannon and Bossone, 1986; Hannon and Skala, 1982; Sondeen et al., 1989a)* and urea *(Hannon and Bossone, 1986; Hannon and Skala, 1982)*. These changes suggest an increase in protein catabolism, although it seems probable that most, if not all, of the increases in urea and creatinine are attributable to reduced renal clearance *(Hannon and Skala, 1982; Shackford et al., 1988b; Sondeen et al., 1989b)*. The contributions of amino acids to energy metabolism and gluconeogenesis, and the role played by glucocorticoids, need to be investigated. This author is aware of only one study that dealt with hemorrhage-induced changes in the intermediary lipid metabolism of swine. Boncompagni et al. *(1968)* report hemorrhage-induced decreases in plasma free fatty acid concentrations in neonatal but not in suckling pigs.

Temperature Regulation

Because of the above indicated changes in total body energy metabolism, one might expect alterations in body thermal status during hemorrhagic hypotension. Although this subject has not been studied definitively, we do know that fixed volume-blood loss in conscious pigs can lead to an elevated core temperature *(Carlson et al., 1989; Weiskopf et al., 1986)*, a change that suggests an increase in body heat content. Conversely, core temperature tends to decrease in anesthetized pigs subjected to hemorrhage *(Metzger et al., 1986; Rowe and Uribe, 1972)*, a change that suggests a reduction in body heat content. At first glance, one might attribute these apparent changes in body heat content to increases or decreases in heat production, but such a conclusion does not account for potential changes in body heat loss. An increase in heat loss, for example, will produce a decrease in heat content even though heat production remains constant. Appropriate measurements are needed to precisely describe the effects of hemorrhage on all major avenues of body heat dissipation in pigs, most importantly from the skin and respiratory tract.

BLOOD GAS AND ACID BASE STATUS

The disparity between O_2 delivery and O_2 demand and resultant lactacidemia leads to an increased hydrogen ion load in the blood and tissues. During the earlier stages of severe hemorrhage, this load is effectively neutralized with bicarbonate buffer and ventilatory elimination of the CO_2 so produced (Fig.5). Bicarbonate losses are thus matched by appropriate decrements in PCO_2 so that

plasma ratio of bicarbonate to carbonic acid remains reasonably constant and arterial pH is maintained within the normal range (Fig. 5). In many conscious animal preparations, maintenance of a near normal ratio of bicarbonate to carbonic acid persists over the entire hemorrhage episode, and little or no change in arterial pH is observed *(Armstead et al., 1988; Bellamy et al., 1984b; Hannon and Bossone, 1986; Maningas et al., 1986; Traverso et al., 1986b, 1987; Wade et al., 1988)*. As illustrated in Fig. 5, lethal hemorrhage can lead to a terminal decline in arterial pH (Fig. 5), possibly because ventilatory removal of excess venous CO_2 becomes a limiting factor. If the lethal model involves rapid blood loss, a terminal pH decline may occur subsequent to, but not during, hemorrhage *(Maningas et al., 1986)*.

If anesthetized pigs are allowed to breathe spontaneously, they often show a decrease in arterial pH during hemorrhagic hypotension *(Angelakos and Bonner, 1979; Bonner et al., 1978; Noble, 1975; Reddy et al., 1974; Rowe and Uribe, 1972)*. This decrease is due, presumably, to an anesthesia-induced attenuation of the hyperventilatory response to the lactacidemia. As a consequence, the excess CO_2 generated by bicarbonate breakdown is not adequately eliminated by ventilation, and the plasma ratio of bicarbonate to carbonic acid will decrease *(Hannon et al., 1989a; Pfenninger et al., 1985)*. To offset this defect, most investigators mechanically ventilate their anesthetized animals. Oftentimes, the objective of such ventilatory regulation is not stated, or the selected objective may not simulate the acid-base responses seen in conscious animals. In some instances, for example, ventilation is regulated to maintain a constant arterial PCO_2, but under this circumstance plasma bicarbonate losses during hemorrhage are not matched with comparable decrements in CO_2. The ratio of plasma bicarbonate to carbonic acid therefore decreases with a resultant fall in arterial pH *(Laptook et al., 1983; Mäkisalo et al., 1988; Matsuda et al., 1988; Norton et al., 1972)*. A more rational approach, at least in terms of simulating the characteristics of conscious animals, would be to regulate ventilation to maintain a constant arterial pH.

Although blood buffers other than bicarbonate appear to play only a minor role in the regulation of acid-base status during hemorrhage, the concentrations of these buffers decrease progressively as blood losses mount *(Hannon et al., 1989a)*. These buffers, hemoglobin and plasma protein anion, are diluted by the transcapillary movement of water from the extra- to the intravascular space. Such dilution, coupled with the decline in bicarbonate concentration, produces a progressive deterioration of blood buffer base concentration *(Hannon et al., 1989a)*. Loss of buffer base, particularly the bicarbonate component (Fig. 5) may

contribute to the compensatory limitations seen in conscious animals subjected to lethal levels of blood loss. In short, future studies may show that buffer availability for the neutralization of lactic and other metabolic acids becomes a limiting factor in acid-base regulation during severe blood loss.

ELECTROLYTE METABOLISM

Pigs subjected to severe, but nonlethal, blood loss show little or no change in the plasma concentrations of sodium, chloride or phosphate while bicarbonate and plasma protein anion, as indicated above, decrease *(Hannon and Bossone, 1986; Hannon and Skala, 1982; Maningas et al., 1986; Peters et al., 1986; Traverso et al., 1987)*. These animals also exhibit an elevated plasma magnesium concentration and a reduced plasma potassium concentration, the former effect reflecting cellular loss, the latter cellular uptake *(Hannon and Bossone, 1986)*. The lowering of plasma potassium concentration may be related to an increase in cellular glucose utilization *(Hannon and Skala, 1982; Stremple et al., 1976)*.

Pigs subjected to the Wiggers procedure often show electrolyte changes during hypotension that are just the opposite of those seen during fixed-volume hemorrhage. Thus, increases in plasma potassium *(Becker et al., 1977; Fredlund et al., 1974)* and phosphate concentrations *(Wright and Henderson, 1975)* are sometimes observed during prolonged hemorrhagic hypotension. The potassium increments are attributable, presumably, to a deterioration of sodium/potassium pump activity, the phosphate increments to intracellular breakdown of organic phosphates and high energy phosphates. These effects are seen only rarely *(Shackford et al., 1988a)* during fixed-volume hemorrhage. At least in swine, little is known about the specific tissues contributing to the foregoing hemorrhage-induced distortions in total body electrolyte metabolism.

ENDOCRINE RESPONSES TO HEMORRHAGE

Lethal hemorrhage in the conscious pig produces a variety of endocrine changes ranging from activation of the sympathoadrenal axis to an increased release of vasoactive hormones. In our progressive fixed-volume hemorrhage model, plasma renin activity is the first to show a significant increase, followed in turn by epinephrine and norepinephrine, vasopressin, aldosterone, ACTH, and finally cortisol (Fig. 6). Some endocrine responses, such as the rise in ACTH concentration and plasma renin activity, reach maximum levels during the hemorrhage episode while others, such as epinephrine and cortisol, continue to rise after hemorrhage is

terminated. ACTH is unique, showing a decrease from maximal levels during the terminal stages of lethal hemorrhage. This terminal regression may reflect exhaustion of pituitary ACTH stores. In our conscious, lethal model, the magnitude of hormonal responses ranges from 8-fold in the case of ACTH to well over 100-fold in the case of vasopressin, epinephrine and norepinephrine; epinephrine, for example, rose from 137 $\pm$ 31.9 to 23,960 $\pm$ 3597 pg/ml.

Although differences in magnitude and pattern of response are sometimes apparent, most of the foregoing hormonal changes are at least qualitatively similar to those observed by many others in both fixed volume and Wiggers models of hemorrhagic hypotension. Increases in plasma ACTH are thus reported by Carlson et al. *(1989)* and O'Benar et al. *(1987)*, cortisol by Carlson et al. *(1989)*, Norton et al. *(1972)* and O'Benar et al. *(1987)*, vasopressin by Biermann et al. *(1979)*, Carlson et al. *(1989)*, Leffler et al. *(1986)*, Macdonald et al. *(1986)*, Shackford et al. *(1988a, 1988b)* and Weiskopf et al. *(1986)*, plasma renin activity by Binder et al. *(1986)*, Carlson et al. *(1989)*, Maier et al. *(1981)*, Pipkin et al. *(1981)*, Shackford et al. *(1988a, 1988b)*, and Weiskopf et al. *(1984, 1986)*, and catecholamines by Carlson et al. *(1989)*, Rudehill et al. *(1987)*, Shackford et al. *(1988a, 1988b)*, and Weiskopf et al. *(1984, 1986)*. Insofar as can be determined, no one else has investigated plasma aldosterone changes during hemorragic hypotension in pigs.

Elevated plasma levels of numerous other humoral, or humorally related materials also are seen in hemorrhaged pigs. These include beta endorphin *(O'Benar et al., 1987)*, insulin *(Revhaug et al., 1985; Stremple et al., 1976; Wright and Henderson, 1975)*, somatostatin *(Jenssen et al., 1986; Revhaug et al., 1985)*, pancreatic polypeptide *(Revhaug et al., 1985)*, secretin *(Revhaug et al., 1985)*, neuropeptide Y *(Rudehill et al., 1987)*, atrial natriuretic factor *(Shackford et al., 1988b; Ziegler et al., 1987)*, motilin *(Jenssen et al., 1986)*, urinary kallikrein *(Binder et al., 1986; Maier et al., 1981)*, and gastric inhibitory peptide *(Revhaug et al., 1985)*. Plasma levels of some vasoactive materials, such as vasoactive intestinal peptide *(Revhaug et al., 1985, 1988)*, appear to be unaffected by hemorrhage.

As might be anticipated, rate of blood loss can influence the pattern and magnitude of endocrine changes that are induced by hemorrhage. The data of Carlson et al. *(1989)* thus show that maximum increases in hormonal concentrations may occur subsequent to hemorrhage if a fixed volume of blood is removed rapidly *(Carlson et al., 1989)*. Similarly, Carey et al. *(1972)* observe marked increases in adrenal epinephrine secretion when 30% of the

estimated blood volume is removed over 30 min, but no change in secretion when the same amount of blood is removed over 85 min.

Under otherwise comparable experimental conditions, hormonal changes seen with small blood losses are not as great as those seen with large blood losses. Accordingly, the data on conscious, physically restrained pigs reported by Carlson et al. *(1989)* show hemorrhage-induced increments in epinephrine, norepinephrine, ACTH, cortisol, vasopressin and plasma renin activity that are far less than those recorded in Fig. 6.

Other experimental variables have effects that are not readily understood. Physical restraint, for instance, enhances hormonal responses to hemorrhage. Accordingly, with nearly identical hemorrhage protocols, O'Benar et al. *(1987)* report increases in ACTH and cortisol concentration that are about one-half as great as those shown in Fig. 6; catecholamine responses under the two protocols differ by a factor of 10 (unpublished data). The training schedules used to familiarize pigs with physical restraint also modify outcome. Carlson et al. *(1989)* thus report resting values for catecholamines, ACTH, cortisol, vasopressin and renin activity are significantly higher in poorly trained, as compared to fully trained pigs. More importantly, Carlson et al. *(1989)* show that inadequately trained pigs exhibit marked increases in plasma catecholamine levels during hemorrhage while more thoroughly trained pigs show no response at all. At the present time there is little information on the hormonal effects of other experimental variables associated with hemorrhage studies. Comparisons need to be made, for example, between conscious and chemically restrained pigs and between fixed-volume and fixed-pressure models.

GASTROINTESTINAL FUNCTION

Information on the gastrointestinal effects of hemorrhage is scanty and largely limited to results obtained in studies of stress ulcer formation. These studies show that the gastric and duodenal ulcers often found in humans following trauma and hemorrhage *(Eiseman and Heyman 1970; Stremple et al., 1973)*, can be readily simulated in porcine models *(Becker et al., 1977; Collan et al., 1977; Goodman and Osborne, 1972; Kivilaakso et al., 1974; Norton et al., 1972)*. Unlike the dog, pigs exhibit both basal and histamine stimulated gastric acid and pepsin secretion which are analogous to those seen in man *(Merritt and Brooks, 1970)*. Microangiographic studies indicate that the basic microvascular anatomy of the porcine stomach also is similar to that of man *(Kivilaakso et al., 1982)*. Following hemorrhage, the stress lesions seen in swine are

essentially the same as those observed in human patients *(Goodman and Osborne, 1972; Kivilaakso et al., 1982; Norton et al., 1972)*. Furthermore, pigs, like man, show spontaneous peptic ulcer disease *(Stremple et al., 1976)*.

The anesthetized Wiggers model, with reinfusion of shed blood, has been used in all studies of hemorrhage-induced stress ulcer formation in swine. These studies show that ulcer formation is attributable to focal ischemia secondary to a reduction in blood flow to the gastric mucosa *(Kivilaakso et al., 1982; Levine et al., 1978, 1979, 1983; Seufert et al., 1979)*. Increased sympathetic discharge is largely responsible for the reduction in blood flow *(Levine et al., 1983; Hottenrott et al., 1978)*, an effect that can be ameliorated by splanchnicectomy *(Levine et al., 1983)*, splanchnic nerve section *(Hottenrott et al., 1978)*, or H_2 receptor antagonists *(Levine et al., 1978, 1979)*. The presence of microthrombi with degranulating thrombocytes and fibrin strands in the splanchnic microvasculature may contribute to the flow reduction *(Collan et al., 1977; Kivilaakso et al., 1982)*. Etiology of the disease includes an increase in gastric permeability to protein *(Taylor et al., 1979, 1980)*, a cessation of gastric motility followed by copious reflux of bile and duodenal contents into the stomach, focal mucosal hematomas and superficial erosions during or shortly after the shock episode *(Kivilaakso et al., 1974)*. Gastric acid secretion may be unaffected *(Norton et al., 1972)* or increased *(Taylor et al., 1980)*. Somewhat later (i.e., 24 hours) ulcers and areas of hemorrhagic gastritis are seen *(Kivilaakso et al., 1974)*. Porcine stress ulcer formation can be prevented by prefeeding an elemental diet *(Voitk et al., 1972)*. Fluorholmen et al. *(1985)* investigated effects of fixed-pressure hemorrhagic shock as it might be induced by gastrointestinal bleeding. They report evidence of an increase in circulating trypsin activity, a response that suggests acute pancreatitis is being induced by hemorrhage.

Other than a decrease in tissue blood flow (see above) little is known about the gastrointestinal effects of fixed-volume or uncontrolled blood loss. If we are to understand fully the short and long term consequences of hemorrhagic hypotension, we need experimental data on a variety of functions, such as digestion, intestinal motility and the active and passive absorption of nutrients.

RENAL FUNCTION

Hemorrhagic hypotension in pigs, as in other species, leads to a marked reduction in urine flow. This effect is observed in anesthetized animals subjected to the Wiggers procedure *(Coli et*

al., 1981a, 1981b; Jenssen et al., 1986; Revhaug et al., 1985), in animals subjected to continuous blood loss until death *(Binder et al., 1986; Maier et al., 1981)*, and in conscious animals subjected to a fixed-volume hemorrhage *(Linko and Mäkeläinen, 1988; Shackford et al., 1988a, 1988b; Sondeen et al., 1989b)*. Oliguria is largely, if not entirely, attributable to an increase in renal vascular resistance with a resultant decrease in renal blood flow and glomerular filtration *(Binder et al., 1986; Maier et al., 1981; Shackford et al., 1988b; Sondeen et al. 1989b)*. Decrements in sodium, potassium, and osmolal excretion also are seen *(Sondeen et al., 1989b)*. In the conscious, chronically instrumented pig, a moderate fixed volume hemorrhage has little effect on filtration fraction, the fractional excretion of electrolytes or free water clearance *(Sondeen et al., 1989b)*. These variables, insofar as can be determined, have not been investigated in other porcine hemorrhage models. Some renal functions such as the renin angiotensin system appear to respond normally during hemorrhagic hypotension.

HEPATIC FUNCTION

Despite reductions in portal vein, and sometimes hepatic artery blood flow (see above), many liver functions do not appear to be seriously compromised during hemorrhagic hypotension. Prolonged fixed-pressure hemorrhage in the anesthetized pig may lead to elevated serum levels of hepatic transaminases, but produces no detectable change in various clinical function tests *(Lamesch et al., 1988)*. Hepatic PO_2, pH and O_2 consumption may decrease *(Korsbäck et al., 1984; Lindberg, 1977; Lindberg and Darle, 1977a, 1977b; Mäkisalo et al., 1988)* during fixed-pressure hemorrhage, but transhepatic pH and PCO_2 measurements indicate little change in the capacity of the liver to remove acid metabolites from circulating blood *(LePage et al., 1984)*. Transhepatic measurements also show an undiminished capacity for the liver to remove lactate during hemorrhagic hypotension *(Mäkisalo et al., 1988)*, and a retention of epinephrine-induced blood glucose mobilization from liver glycogen *(Carey and Wallack, 1970; Wright and Henderson, 1975)*. In contrast to these findings, Shi et al. *(1986)* report a decrease in hepatic glutathione content 6 hours after an acute fixed-volume hemorrhage and interpret this change as indicative of a reduced capacity to remove metabolites that would be injurious to hepatic cells. The effects of hemorrhagic hypotension on many other liver functions, such as gluconeogenesis, urea formation and bile formation, have received little attention in porcine models.

CENTRAL NERVOUS SYSTEM FUNCTION

The effects of hemorrhage on the central nervous system function have been studied in some detail in neonatal pigs, but only occasionally in more mature animals. The anesthetized newborn pig responds to brief bouts of fixed-volume blood loss with baroreceptor-mediated responses that are essentially the same as those seen in older pigs *(Gootman 1986; Gootman et al., 1981, 1983, 1986)*. With more severe fixed-pressure hemorrhage, Laptook et al. *(1983)* report decreases in cerebral blood flow and O_2 delivery in anesthetized neonatal piglets that are mechanically ventilated to maintain a constant arterial PCO_2 of 35 torr; the decrements were greatest in the cerebrum, less in the cerebellum and least in the brain stem. These effects may be due, at least in part, to the acidosis that results from the maintenance of normocapnia during hemorrhagic hypotension (see above). Thus, Matsuda et al. *(1988)* report a normal rate of cerebral O_2 consumption during the early stages of severe fixed-pressure hemorrhage in anesthetized, neonatal pigs, and observe decrements in O_2 consumption only when the hypotensive period is prolonged. The eventual decline in O_2 consumption was associated with severe, uncompensated lactacidosis. Furthermore, Leffler et al. (*1986*) report unaltered blood flows to nine different brain areas in conscious neonatal pigs that were subjected to a similar level of hemorrhagic hypotension but ventilated to maintain a constant arterial pH; these pigs also showed an unaltered cerebral O_2 consumption.

The prostanoid system may participate in the maintenance of cerebral blood flow and O_2 consumption during hemorrhage *(Armstead et al., 1988; Leffler et al., 1986)*, but this system does not appear to mediate the increase in vasopressin secretion that is also observed during hemorrhage of neonatal pigs *(Leffler et al., 1987)*. Recent studies of neonatal pigs suggest that cerebral circulatory responses to vasopressin are tone dependent and that prostanoids modulate constrictor responses but are not involved in dilator responses *(Armstead et al., 1989)*.

In older pigs, we observe dizziness and nausea when the conscious, unrestrained animal is subjected to severe, but nonlethal, blood loss (unpublished observations). These changes suggest cerebral hypoxia, but there is little objective evidence to support this interpretation. Older pigs subjected to severe levels of blood loss respond with hyperventilation, tachycardia and a redistribution of cardiac output to vital organs including the brain (see above); hypoxia, if it occurs, does not materially impair these centrally mediated functional responses that are critical to survival. More objectively, Shackford et al., *(1988a)* report little change in EEG

activity of conscious pigs subjected to modest fixed volume hemorrhage. Brain blood flow may decrease during a rapid and potentially lethal fixed-volume hemorrhage, but following hemorrhage it quickly reverts to control levels without any resuscitative treatment *(Bellamy et al., 1984b)*. Other studies show that blood flow to various brain areas remains unaltered in anesthetized pigs that are subjected to the Wiggers procedure but mechanically ventilated to maintain a slightly alkaline arterial pH *(Laughlin, 1983)*. Furthermore, stepwise reductions in the mean arterial pressure of anesthetized pigs do not produce any appreciable change in spinal cord PO_2 until a pressure of 50 torr is reached *(Metzger et al., 1986)*. The foregoing studies suggest that cerebral O_2 delivery remains relatively unimpaired during hemorrhagic hypotension. However, actual measurements of O_2 delivery to the central nervous system have not been reported for hypotensive pigs that are beyond the neonatal stage of development.

Studies in more mature animals do show that hemorrhagic hypotension leads to changes in intracranial pressure, but the functional impact of these changes has yet to be explored. Conscious pigs subjected to a modest (28 ml/kg) fixed-volume blood loss thus exhibit a decrease in intracranial pressure that more or less parallels the decrease in mean arterial pressure *(Shackford et al., 1988a)*. When anesthesia is used, intracranial pressure increases if the animals are allowed to breathe spontaneously and become hypercapnic; mechanical hyperventilation to eliminate the excess CO_2 prevents this effect *(Pfenninger et al., 1984, 1985, 1986)*. The functional consequences of increases or decreases in intracranial pressure have yet to be explored in hypotensive swine.

FACTORS AFFECTING SURVIVAL

Survival of conscious pigs following fixed-volume hemorrhage is determined by the severity of hemorrhage insult and the effectiveness of normal compensatory response elicited either directly or indirectly by hypotension. Critical compensations include amelioration of the decrements in venous return by muscle activity, increased arterial O_2 extraction, redistribution of blood flow in favor of vital organs, effective buffering of lactic acid, hyperventilation, and restoration of blood volume by transcapillary refill. In uncontrolled hemorrhage, survival depends upon sharp reductions in cardiac output, mean arterial pressure and peripheral resistance. These responses limit blood loss and facilitate rapid clot formation at the site of vascular rupture *(Bickell et al., 1989)*.

When normal compensatory responses fail, death ensues. The agonal phase, at least in the author's laboratory, is characterized by a progressive exacerbation of lactacidemia (Fig. 5), a deterioration of ventilatory function, and finally a cessation of myocardial activity. The factors responsible for this sequence of events are not totally understood. Inadequate perfusion of vital organs does not appear to be a critical variable *(Bellamy et al., 1984b)*, hence a deterioration of myocardial function is not the immediate cause of death. Uncompensated lactacidosis, attributable to inadequate perfusion of the viscera and carcass *(Bellamy et al., 1984b)*, seems to be a critical variable and may precipitate, either directly or indirectly, the deterioration in ventilatory function that precedes death. In fact, survival or nonsurvival of conscious pigs can be predicted with a high degree of confidence by the level of lactacidemia recorded at the end of hemorrhage *(Wade and Hannon, 1988)*.

As indicated in earlier sections of this review, certain experimental variables produce qualitative or quantitative alterations in the normal compensatory responses to hemorrhage. Some of these alterations have an adverse effect on survival. Anesthetized pigs, for example, are far less tolerant of fixed volume hemorrhage than conscious pigs, in part because of distortions in the normal redistribution of cardiac output in favor of vital organs *(Simon and Olsen, 1969a, 1969b)*. Uncompensated lactacidemia, attributable to inadequate ventilation during anesthesia, may be a contributing factor. Other critical variables include the magnitude and rapidity of blood loss. Rapid removal of blood produces a more profound hypotension than the same amount removed slowly *(Traverso et al., 1984)*, probably because less time is available for transcapillary refill to replenish blood losses. Prior dehydration may also compromise transcapillary refill, hence the tolerance to blood loss *(Barrientos et al., 1982)*. Splenectomy, hyperthermia, and physical restraint of the naive pig significantly alter hemodynamic responses to hemorrhage *(Wade and Hannon, 1988)*. Restraint, furthermore, even when the animals are highly trained to accept such procedures, has a major effect on survival. The unrestrained pigs used for illustrative purposes in an earlier review *(Hannon and Bossone, 1986)*, for instance, were subjected to essentially the same hemorrhage protocol as the restrained pigs used to illustrate the present review; all of the former animals survived the hemorrhage episode, all of the latter died. Critical factors responsible for the poorer performance of restrained pigs are not fully understood, but seem to be related to the degree of lactacidemia that is elicited by hemorrhage. The Wiggers procedure, particularly with reinfusion of shed blood, leads to numerous alterations in normal compensatory responses. Many of these are attributable to compromised capillary flow brought on by platelet aggregation or fibrin formation

(Burghuber et al., 1977; Collan et al., 1977; Kivilaakso et al., 1982; Pressler et al., 1980). Some experimental variables that might be expected to affect outcome fail to do so. Alcohol intoxication, for instance, may enhance hypotension during the early stages of lethal blood loss but does not affect survival time *(Zink et al., 1988)*.

RESUSCITATION

Pigs are now being used extensively to evaluate the efficacy of various resuscitation procedures that will ultimately promote survival of the animal by correcting the functional defects associated with hemorrhagic hypotension and shock. Pigs are admirably suited for this purpose since their responses to interventions are remarkably similar to those seen in humans. Most resuscitation procedures fall into two general categories: 1) the use of pharmaceutical agents to reverse one or more dysfunctions, and 2) the use of crystalloid or colloid solutions to restore blood volume and (as a consequence) to return hemodynamic and other functions to normal levels. Exceptions to these categories include the use of positive end expiratory pressure ventilation to improve blood oxygenation and hemodynamic functions *(Ahnefeld et al., 1984)*, use of the Military Antishock Trousers (MAST suit) to enhance perfusion of vital organs such as the heart and brain *(Bellamy et al., 1984a; Traverso et al., 1985b)*, use of autotransfusion of whole blood in a clinical surgical setting *(Solem et al., 1986)*, and use of splanchnicectomy to increase gastric blood flow and prevent stress ulcers formation *(Hottenrott et al., 1977; Levine et al., 1983)*.

Pharmaceutical Interventions

The objectives of pharmaceutical interventions are varied and and oftentimes directed at specific functional defects. For example, Levine et al., (1978, 1979) and Taylor et al., (1979) report beneficial effects of Cimetidine, an H_2 antagonist, in enhancing blood flow to the gastric mucosa during fixed-pressure hemorrhagic hypotension, an effect that would improve resistance to gastric ulceration. An H_1 receptor antagonist, diphenhydramine, is ineffective in this regard *(Levine et al., 1979)*. Improved blood flow to the gastric mucosa is also seen following topical administration of 16,16-dimethyl prostaglandin E_2 *(Gaskill et al., 1984b)*, but not following topical administration of prostaglandin F_{2a} *(Gaskill et al., 1984a)*. Vasopressin, which is sometimes used in the emergency treatment of esophageal and intestinal bleeding, is contraindicated during fixed-pressure hemorrhagic hypotension; it exacerbates hepatic and intestinal ischemia and may increase the risk of hypoxic intestinal lesions *(Korsbäck et al., 1984)*.

Glucocorticoids partially ameliorate the metabolic defects and cellular damage associated with the development of irreversible shock following prolonged fixed-pressure hemorrhage. Using such a model, Nagasue et al. *(1974)* and Fredlund et al. *(1972, 1974)* show that hydrocortisone administration reduces metabolic acidosis, supresses the hyperkalemia, and attenuates the release of cellular acid hydrolases to the circulating blood. Methylprednisolone appears to be effective in treating the disseminated intravascular coagulation (DIC) that is seen in a combined injury model that incorporates fixed-pressure hemorrhage and trauma, the latter being simulated by infusion of frozen and subsequently thawed blood *(Hardaway et al., 1987; Williams, 1986)*. Other agents directed at specific objectives include the use of glucagon *(Lindberg and Darle, 1977a)* and Dextran-40 *(Lindberg and Darle, 1977b)* to improve hepatic artery blood flow and liver oxygenation during prolonged fixed-pressure hemorrhage, and the use of hypertonic glucose to improve myocardial oxygenation during severe fixed-volume hemorrhage *(Stremple et al., 1976)*.

Swine are also being used in a more general sense to evaluate the efficacy of pharmaceutical resuscitation procedures that are directed at ameliorating, or reversing, the total body dysfunctions that eventually lead to death. An example of this use is seen in the report of DiStazio et al. *(1980)*, which describes beneficial effects of ATP-$MgCl_2$ in conscious pigs subjected to a rapid and severe fixed-volume hemorrhage. The benefits included improvements in hemodynamic and metabolic status, and a prolongation of survival time. Addition of glucose or mannitol did not enhance the results obtained with ATP-$MgCl_2$ alone. Salerno et al. *(1981)* report favorable responses to naloxone, an opioid antagonist, in anesthetized, mechanically ventilated pigs subjected to fixed-pressure hemorrhage; improvements included an increase in peripheral resistance and blood pressure, but no alteration in cardiac output. Beneficial effects of naloxone are not seen in conscious pigs subjected to a lethal fixed-volume hemorrhage. In such a model, the adrenergic hemodynamic responses, indirectly due to naloxone, further impair tissue perfusion and reduce survival time *(Traverso et al., 1985a)*. Naloxone, furthermore, does not reverse decrements in myocardial performance seen in the hypoperfused porcine heart *(Heydorn et al., 1985)*. Varied results are reported on the use of drugs that alter vasoactivity during hemorrhagic hypotension. Administration of phenoxybenzamine, an alpha adrenergic blocker, improves the survival of anesthetized pigs subjected to fixed-pressure hemorrhage *(Angelakos and Bonner, 1979)*. Administration of norepinephrine to similarly treated animals improved survival time but not survival incidence *(Angelakos and Bonner, 1979)*. Metaraminol, a vasopressor, has a favorable effect on myocardial

capillary flow when administered to anesthetized pigs subjected to fixed-volume hemorrhage, but when administered to similarly hemorrhaged conscious pigs it decreases capillary flow in most vascular beds, including capillaries supplied by the coronary arteries *(Olsen, 1969)*. In a rather curious paper describing results obtained in one pig subjected to fixed-volume blood loss, McIlroy et al., *(1986)*, report an improvement in blood pressure following administration of a 50cc bolus of hydrogen peroxide. They attribute this effect to improved tissue oxygenation but provide no supporting data. Since uncompromised lactacidosis may lead to death, Syverud et al. *(1987)* evaluated the effectiveness of dichloroacetate in reducing lactate production during severe hemorrhagic hypotension; their attempt was unsuccessful.

Resuscitation with Crystalloids

In this country, hemorrhagic hypotension in human trauma victims is commonly treated with either whole blood, crystalloid solutions, or both. Colloids are popular in Europe. The objective of such treatment is to restore circulating blood volume, cardiac output, arterial pressure and O_2 transport to levels compatable with survival. Blood transfusions are highly effective in achieving this objective and serve as the standard against which the efficacy of alternative resuscitation solutions can be compared in animal models. In an otherwise lethal porcine model, for example, 90% survival is achieved following resuscitation with a volume of autologous blood that is equal to the volume of blood lost *(Traverso et al., 1986b)*. In contrast, only 25% survival is achieved in this model following resuscitation with an equivalent volume of isotonic saline *(Traverso et al., 1986a, 1986b)*.

In porcine models, as in human trauma patients, efficacy of resuscitation with conventional crystalloids depends upon the volume and composition of the solution that is administered. Volume dependence is clearly demonstrated in a report by Traverso and his colleagues *(1986b)*, showing progressive improvements in survival following 14, 100 and 300% replacement of shed blood with isotonic saline. These investigators also demonstrate composition dependence, showing that resuscitation with Ringer's lactate leads to significantly greater survival than resuscitation with Plasmalyte A. Plasmalyte A is a proprietary Ringer's solution containing acetate and gluconate as partial anion substitutes for chloride. Although volume of administered crystalloid solution is an important variable, rate of administration, according to Chudnofsky et al. *(1989a)*, may have little effect on outcome. In a porcine model of prehospital management, these investigators show that early intravenous infusion of normal saline does not enhance hemodynamic status, arterial O_2 delivery or ultimate survival.

Resuscitation with Colloids

Because large amounts of conventional crystalloid solutions are needed to restore blood volume and hemodynamic status, undesireable side effects may arise. Edema, attributable to fluid transfer from the intra- to extravascular space, is one such problem. Colloidal resuscitation solutions minimize this fluid transfer because the oncotic properties of the solute promote vascular retention of the administered resuscitation volume. Compared to crystalloid solutions, far less colloid solution is needed to achieve effective resuscitation. In a conscious model, Traverso and his colleagues *(1986a)* demonstrate that survival following resuscitation with one volume of 5% human serum albumin is equivalent to that observed with 3 volumes of normal saline. In an anesthetized mechanically ventilated model, Linko and Mäkeläinen *(1988)* achieve essentially the same plasma volume expansion with one volume of hydroxyethyl starch-120 or Dextran-70 as they achieve with 4 volumes of Ringer's acetate. Linko and Mäkeläinen *(1988)* also report superior maintenance of blood volume, body fluid volume and plasma colloid osmotic status following resuscitation with colloidal solutions. In a similar model, Mäkisalo et al. *(1988)* show that resuscitation with hydroxyethyl starch and Dextran-70 produce comparable improvements in hemodynamics, blood gas status, and liver function when administered to anesthetized pigs following fixed-pressure hemorrhage. Significantly less improvement in these variables is seen when the animals are resuscitated with Ringer's acetate *(Mäkisalo, 1988)*. Not all colloid solutions, however, are eqivalent in terms of resuscitative effectiveness; some are clearly more effective than others. Accordingly, Traverso et al. *(1986a)* demonstrate in their lethal hemorrhage model that resuscitation with typed fresh-frozen plasma leads to significantly better survival than resuscitation with 5% albumin. They attribute the difference in effectiveness to the superior acid buffering characteristics of fresh frozen plasma *(Traverso et al., 1985c)*.

Resuscitation with Hypertonic Solutions

At the present time, porcine models are providing valuable information on the efficacy of a new class of resuscitation solutions: hypertonic crystalloid solutions, with and without added colloid. Interest in these solutions stems from the small volume needed to effect resuscitation, and the rapidity with which the resuscitative effects are obtained. First use of moderately hypertonic solutions in pigs is found in a report by Peters et al. *(1986)* who added lactate or mannitol to conventional Ringer's lactate to raise osmotic pressure from about 260 to about 469 mOsm/kg H_2O. When administered to anesthetized, mechanically ventilated pigs bled to obtain a sustained reduction in cardiac output, effective resuscitation required twice as much conventional Ringer's lactate as either of

the two hypertonic solutions. When similarly resuscitated, however, Ringer's lactate and hypertonic Ringer's lactate seem to restore and maintain cardiac output better than hypertonic Ringer's mannitol *(Peters et al., 1986)*. Effectiveness of a moderately hypertonic Ringer's lactate solution, in this instance 514 mOsm/kg H_2O, is reported by Shackford et al. *(1988a, 1988b)*. They describe improvements in renal, cerebral, and pulmonary function in a conscious, nonlethal fixed-volume hemorrhage model following resuscitation to return central venous pressure to control levels. The effectiveness of more concentrated hypertonic solutions (5.0, 7.5, and 10% NaCl) is reported by Traverso and his colleagues *(1987)*. When used in a normally lethal hemorrhage model, they report optimum surivival following replacement of 25% of shed blood with 7.5% (2400 mOsm) NaCl. Survival enhancement is associated with improvements in hemodynamic and acid-base status.

A major problem with hypertonic solutions, in swine as in other species, is that they do not sustain the improvements in function that are seen initially after resuscitation *(Maningas 1987; Wade et al., 1989a)*. Functional deterioration subsequent to resuscitation is attributable to solute and water transfer from the intra- to the extravascular space. To counteract this transfer, a number of workers are now evaluating resuscitation solutions containing a hypertonic component, in most instances 7.5% NaCl, to effect initial fluid transfer to the vasculature, and a colloid component, such as 6% Dextran-70, to promote vascular retention of the fluid so transfered. Remarkably small volumes of these hypertonic/hyperoncotic solutions are needed for effective resuscitation. Thus, Maningas et al. *(1986)*, using a conscious, normally lethal, fixed-volume hemorrhage model, report 100% long-term survival following resuscitation with 4.0 ml/kg bolus of 7.5% NaCl in 6% Dextran-70; 46% of the blood volume was removed during hemorrhage. By comparison, all pigs died following resuscitation with a similar volume of 0.9% NaCl, and intermediate results were observed with 7.5% NaCl or 6% Dextran-70 alone. Maningas et al. *(1986)* show that survival enhancement in pigs resuscitated with hypertonic saline/dextran is associated with sustained improvements in mean arterial blood pressure and acid-base status. In a subsequent report Maningas *(1987)* shows that resuscitation with hypertonic saline/dextran leads to an increase in cardiac output and decrease in peripheral resistance, and presents data showing that these changes produce significant improvements in blood flow to the myocardium, kidneys, liver, small intestine and pancreas, but not to the brain, diaphragm, skin, muscle or fat. In a more severe, conscious, fixed-volume model, Wade et al. *(1989a)* also report significant enhancement of survival following resuscitation with a 4.0 ml/kg bolus of hypertonic saline dextran. The salutory

effects in this instance were at least partly attributable to a sustained vascular expansion which led, in turn, to increases in cardiac output, heart rate, mean arterial pressure, and a transient decrease in peripheral resistance. Small bolus infusions of 2400 mOsm NaCl do not lead to worrisome increases in plasma sodium concentration; the values shortly after injection range from 149 mEq/L *(Wade et al., 1989a)* to 164 mEq/L *(Maningas et al., 1986)*. The data of Hannon et al. *(1989b)* show no major improvement in arterial O_2 delivery following small bolus infusions of hypertonic saline/dextran in a normally lethal hemorrhage model, because improvements in cardiac output are largely offset by decrements in blood O_2 capacity. Their data suggest that survival is enhanced, at least in part, by a decrease in tissue O_2 demand. In a more modest, nonlethal hemorrhage model, Sondeen et al. *(1989a)* report that resuscitation with hypertonic saline dextran produces marked improvements in renal function, including a decrease in renal vascular resistance, increases in renal blood flow, glomerular filtration rate and sodium clearance, and a restoration of urine flow. In an anesthetized, continuous hemorrhage model, Chudnofsky et al. *(1989b)* observe significant improvements in hemodynamic, O_2 delivery and survival variables following resuscitation with hypertonic saline/dextran compared to those seen in animals treated with normal saline.

CONCLUSIONS

Utility of porcine models can be compromised by use of the Wiggers fixed-pressure hemorrhage procedure, particularly if the period of sustained hypotension is followed by reinfusion of shed blood. The fixed-pressure model, in its classical sense, has little clinical relevance, and the reinfusion of shed blood may lead to pathophysiologic changes that are not typically seen in human trauma victims. Use of anesthetics further compromises utility, largely because of their effects on ventilation, acid-base, and hemodynamic variables. Fixed-volume hemorrhage procedures better reflect hemorrhagic hypotension as it is commonly encountered in combat casualties or accident victims, but the data acquired from such models also can be compromised by anesthetic agents. In most instances, however, the conscious fixed-volume model does not replicate all of the clinical characteristics of hemorrhagic hypotension. Lack of a trauma component represents a major deficit that should be addressed, either directly, which may be ethically unacceptable, or indirectly by innocuous simulations of trauma characteristics. If anesthetics must be used to implement an experimental model, efforts should be made to achieve functional

characteristics that are equivalent to those seen in conscious animals.

On the basis of currently available data, the immature pig or the miniature pig appears to be an excellent biomedical model for studies on the physiologic, biochemical and other responses to hemorrhagic hypotension. The pig also provides an excellent model for studies of the pathophysiological consequences of hemorrhagic shock and for efficacy studies of conventional and newly developed resuscitation procedures.

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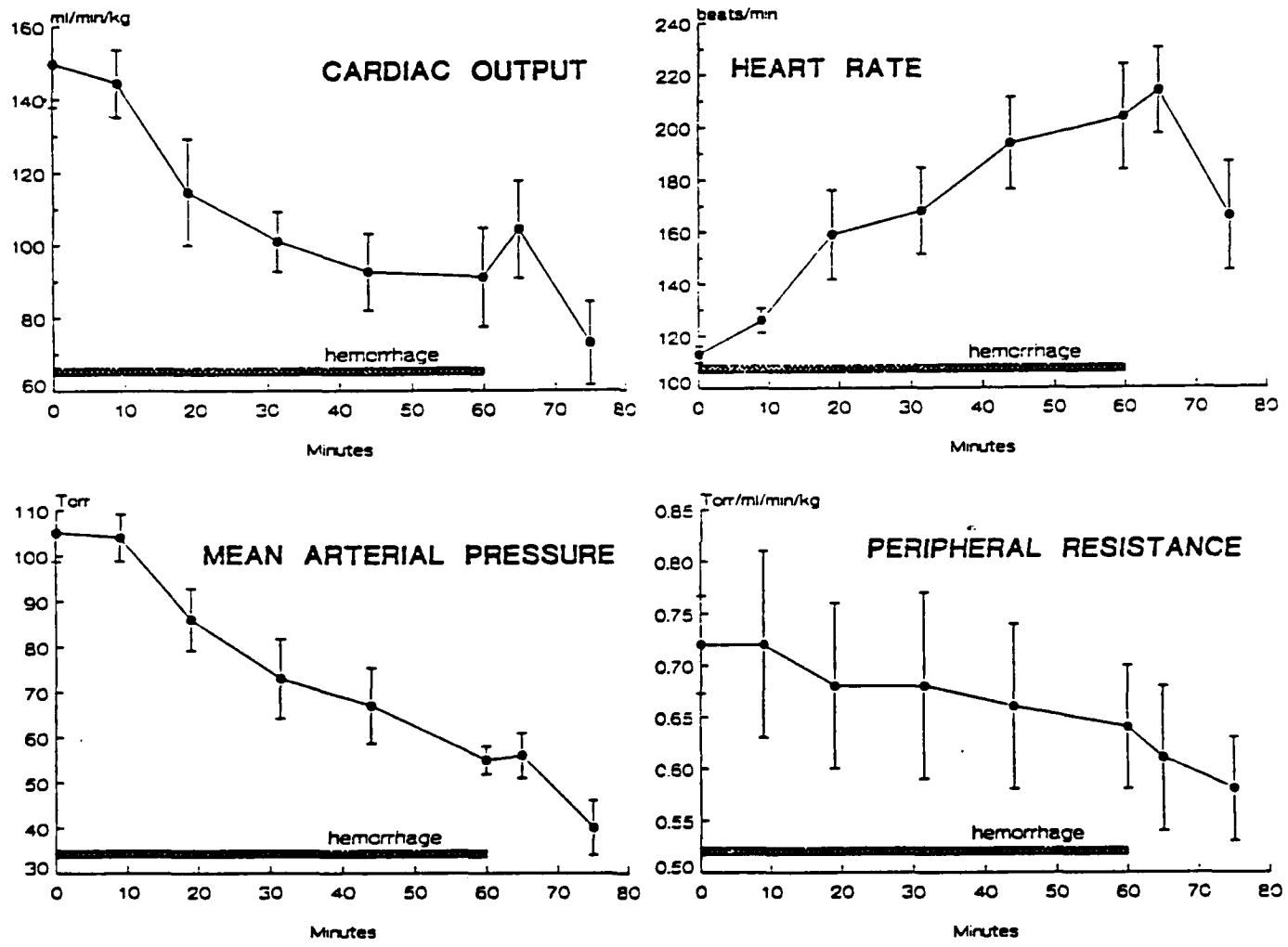
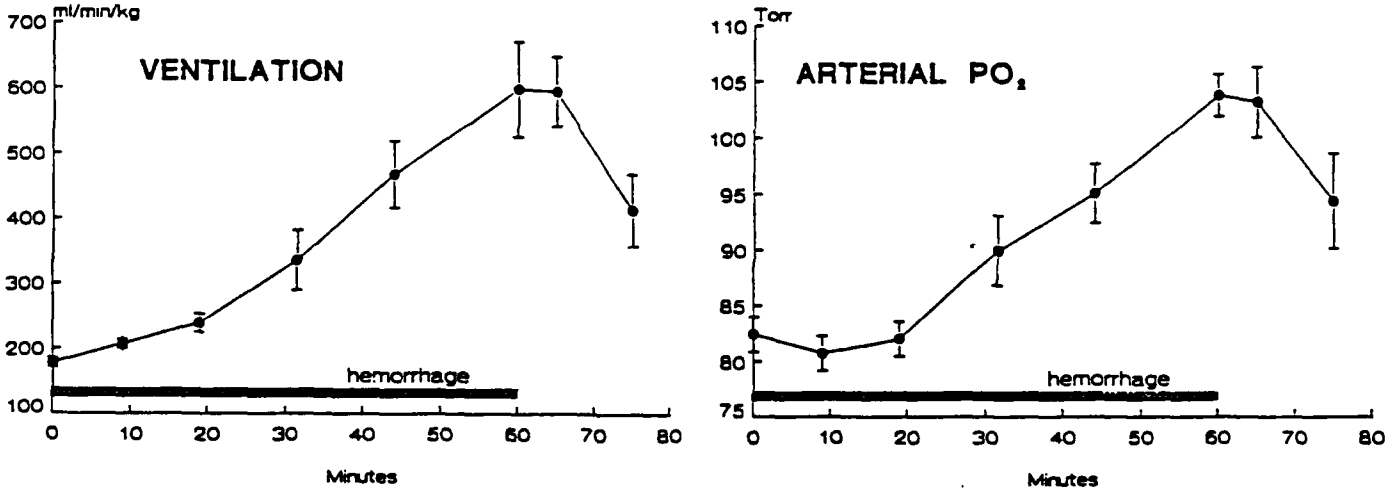
FIGURE 1



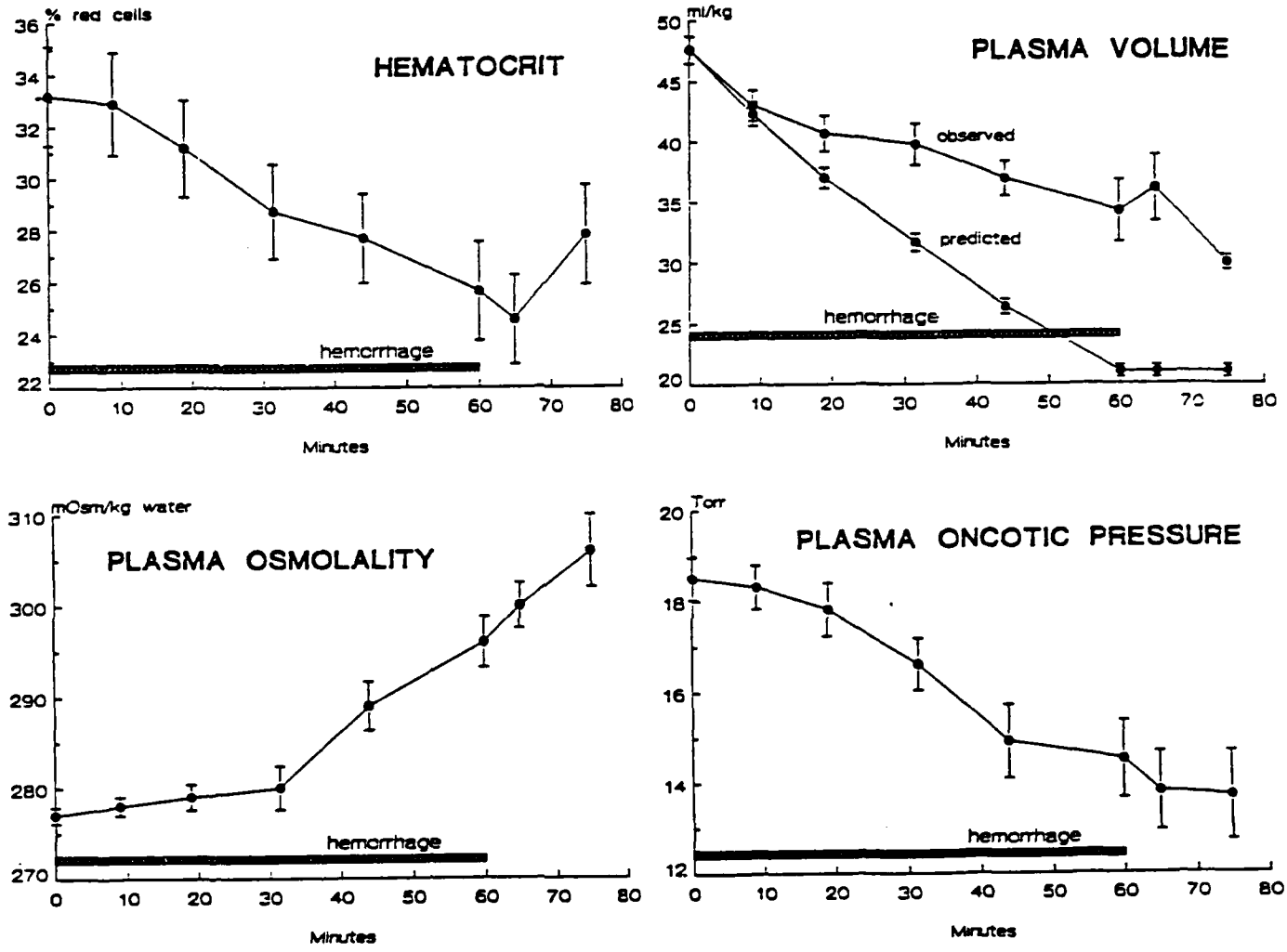
Hemodynamic Effects of Progressive Fixed-Volume Hemorrhage (37.5ml/kg Total) as Measured in Conscious, Chronically Instrumented Pigs.

FIGURE 2



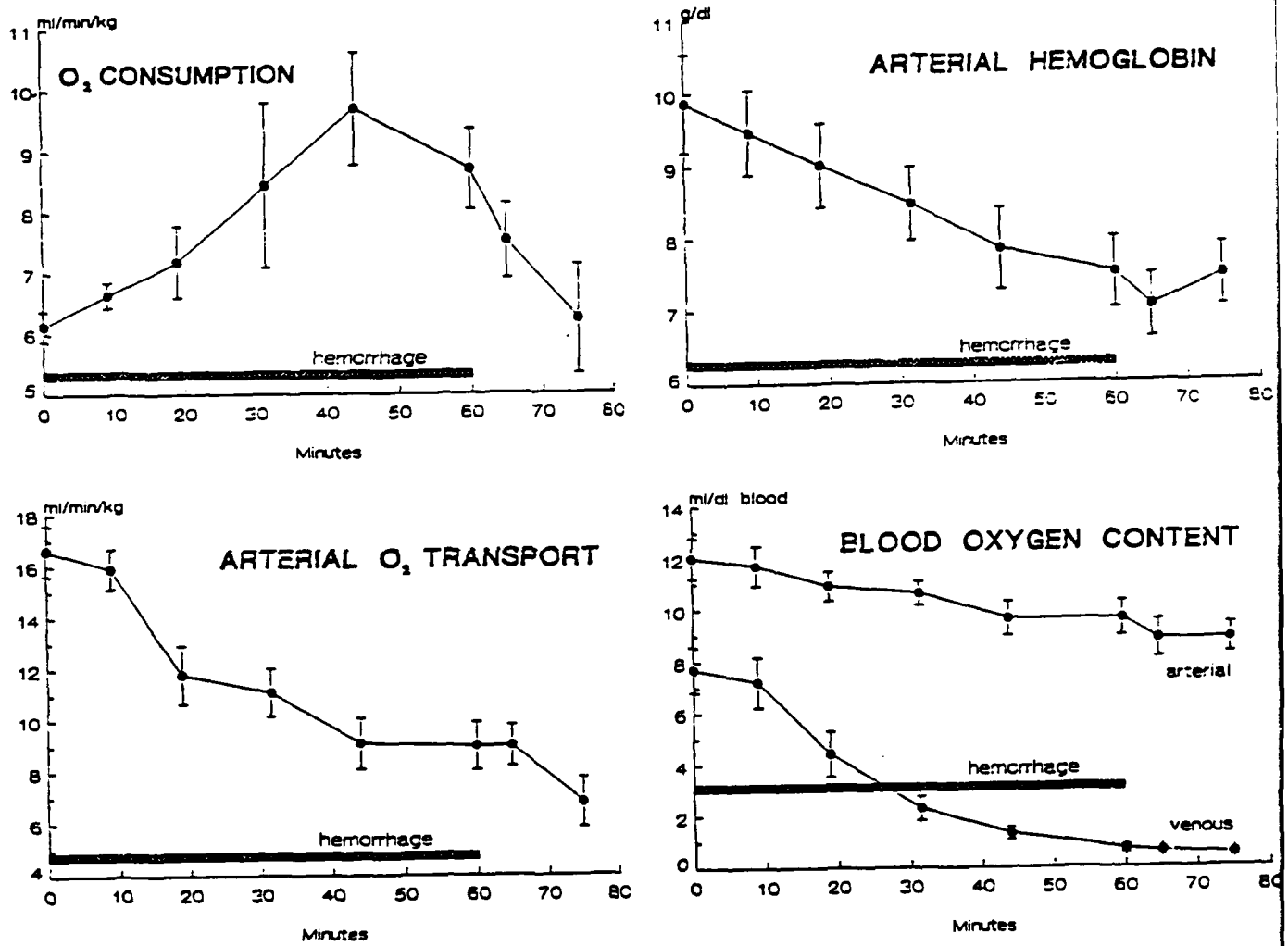
Alterations in Expired Ventilation (BTPS) and Arterial PO_2 During Progressive Fixed-Volume Hemorrhage (37.5 ml/kg Total) as Measured in Conscious, Chronically Instrumented Pigs.

FIGURE 3



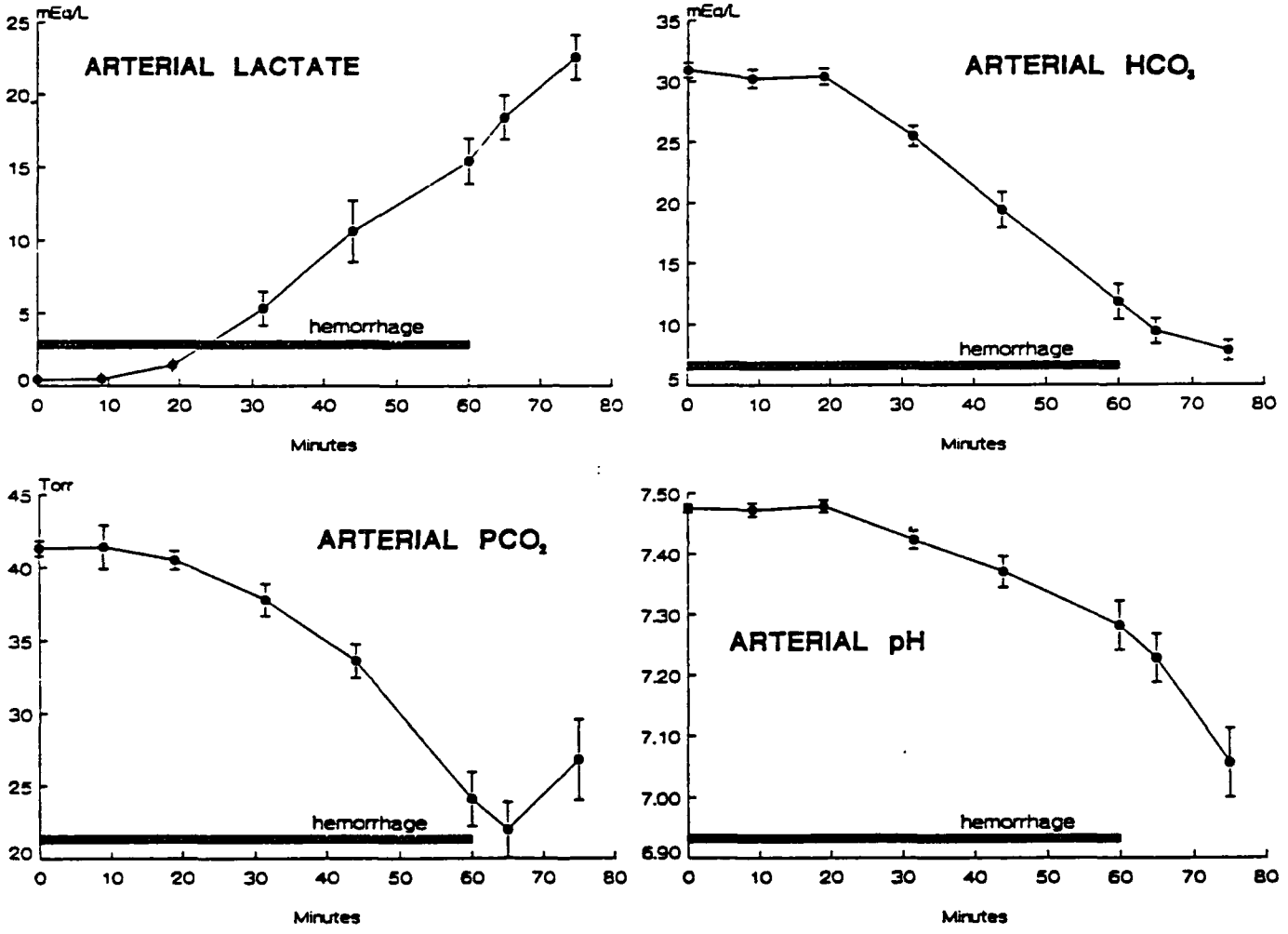
Alterations in Plasma Osmolality and The Effects of Transcapillary Refill on Hematocrit, Plasma Volume and Plasma Oncotic Pressure During Progressive Fixed-Volume Hemorrhage (37.5 ml/kg Total) as Measured in Conscious, Chronically Instrumented Pigs.

FIGURE 4



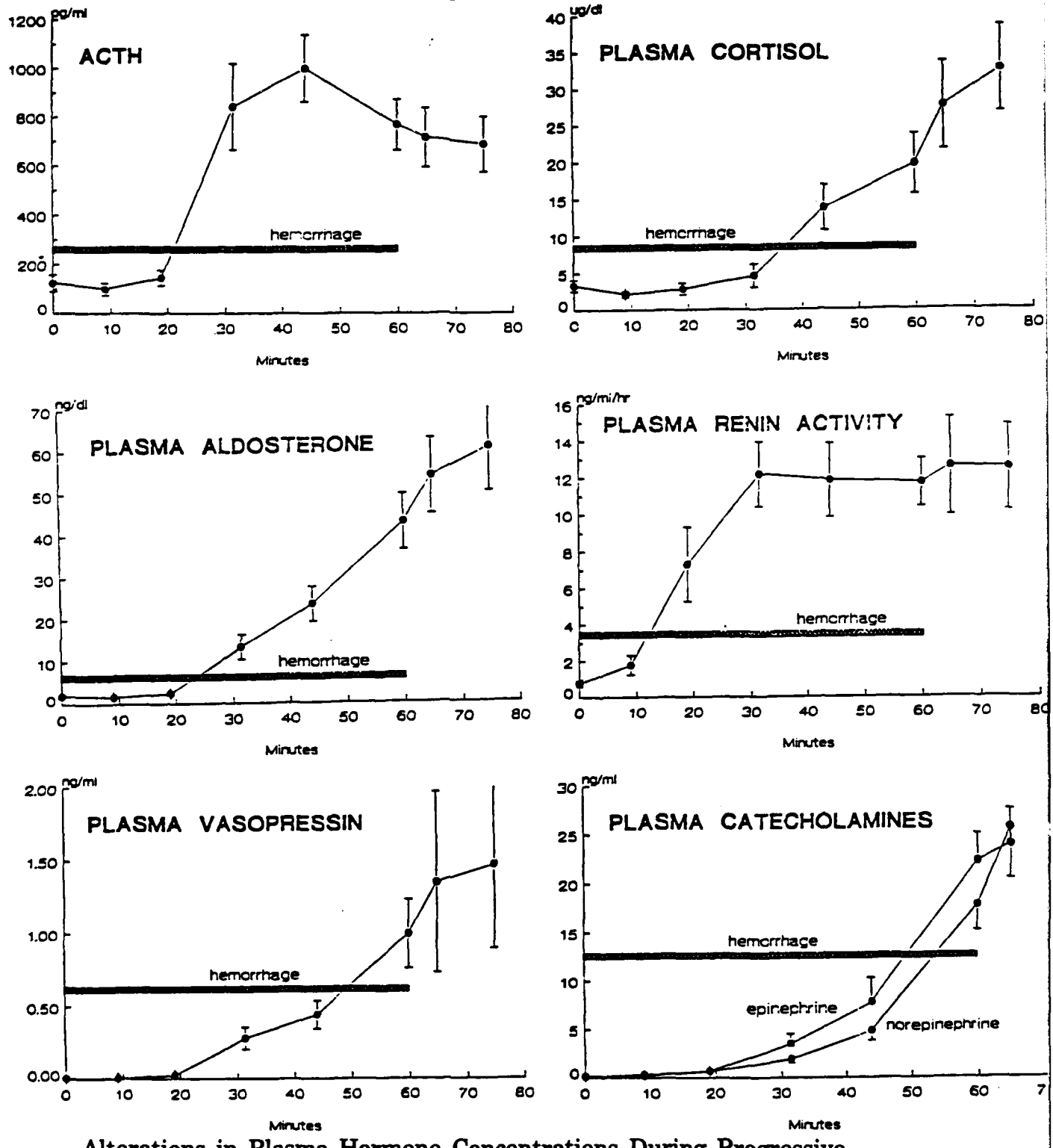
Factors Affecting Oxygen Supply and Demand During Progressive Fixed-Volume Hemorrhage (37.5 ml/kg Total) as Measured in Conscious, Chronically Instrumented Pigs.

FIGURE 5



Acid-Base Changes During Progressive Fixed-Volume Hemorrhage (37.5 ml/kg Total) as Measured in Conscious Chronically Instrumented Pigs.

FIGURE 6



Alterations in Plasma Hormone Concentrations During Progressive Fixed-Volume Hemorrhage (37.5 ml/kg Total) as Measured in Conscious Chronically Instrumented Pigs.

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Head, Biological Sciences Division
OFFICE OF NAVAL RESEARCH
800 North Quincy Street
Arlington, VA 22217-5000

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